colleagues present evidence that UTY can act independently of sex hormones, a more nuanced interplay between UTY and sex hormones is possible and even likely in PAH. Future work to define that complex mechanism may help to unravel the still unsolved estrogen paradox as well as the clinical observation of greater disease severity in males (3).

Ultimately, the fundamental contributions of this study could pave the way for a more precise understanding of the complex PAH network of sex biases across genetic, environmental, immunologic, and metabolic factors (Figure 1; 1, 6, 13, 14). If successful, such endeavors bring us closer to precision medicine in PAH and long-awaited, gender-based clinical treatment strategies in this challenging disease. ■

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Chronic Obstructive Pulmonary Disease–Obstructive Sleep Apnea Overlap: More Than a Casual Acquaintance

In this issue of the *Journal* (pp. 197–205), Sterling and colleagues (1) report on the impact of positive airway pressure (PAP) therapy in patients with overlap syndrome.

Chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA) each affect at least 10% of the adult general population and thus, the two disorders occurring together, often referred to as the overlap syndrome, is likely to be common based on chance association alone. Some factors relating to COPD such as malnutrition leading to low body mass, hyperinflation associated with a low diaphragmatic position (increased "tracheal tug"), reduced REM sleep, upright sleep position, and potentially age factors can decrease the likelihood of OSA. Conversely, other variables such as weight gain, cigarette smoking, medications, rostral fluid shifts in recumbent position, higher diaphragmatic position, etc., can predispose to OSA (2). Additionally, OSA predisposes to lower airway inflammation, which in turn may promote the development of COPD (Figure 1). Both COPD and OSA generate local and systemic inflammatory responses that may lead to cardiovascular morbidity and, thus, the overlap syndrome should be expected to be associated with an increased likelihood of cardiovascular disease compared with either disorder alone (3). While pulmonary hypertension has long been recognized as a common finding in overlap patients, likely due to more severe diurnal hypoxemia than patients with COPD alone (4), epidemiological data on the prevalence of other co-morbidities are limited. However, Kendzerska and colleagues

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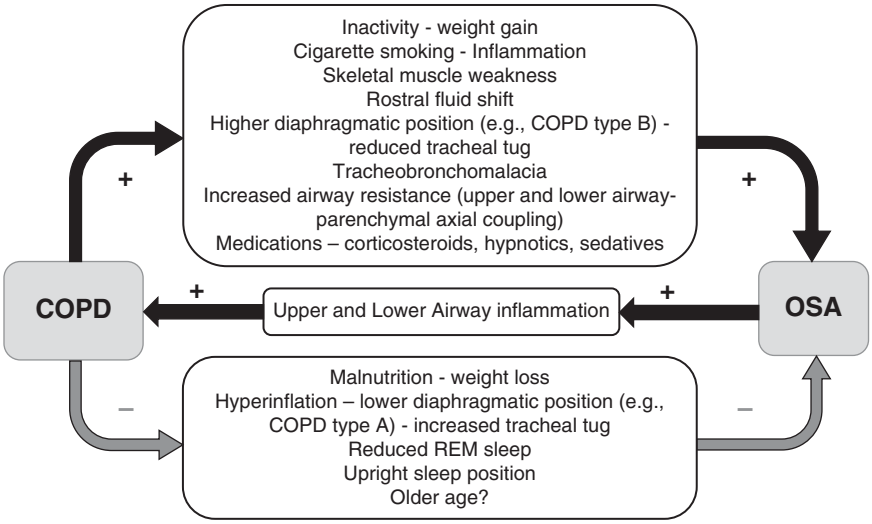

Figure 1. Inter-relationships between chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA), illustrating COPD-related factors that increase (+) or decrease (−) the likelihood of OSA, and OSA-related factors that may promote COPD.

recently reported more severe nocturnal oxygen desaturation in addition to higher rates of cardiovascular morbidity and all-cause mortality in overlap syndrome compared with patients with COPD or OSA alone (5). The importance of recognizing co-existing OSA in patients with COPD is reinforced by a report that, in a rodent model, cardiovascular changes induced by chronic intermittent hypoxia can be reversed by normoxia (6).

The practical implications of the COPD-OSA overlap syndrome include that nocturnal PAP therapy may be part of the management strategy in patients with COPD-OSA overlap, whereas this modality has a lesser role in patients with COPD alone, except in highly selected cases associated with hypercapnic respiratory failure (7). PAP therapy has previously been shown to be associated with improved survival and fewer acute hospitalizations in patients with COPD-OSA overlap when compared with conventional therapy without PAP (8). The report of Sterling and colleagues in the current issue of the *Journal* (1) adds further important data on health outcomes in patients with COPD-OSA overlap by demonstrating that patients with the overlap syndrome who were adherent to PAP therapy had significantly better health outcomes as measured by significantly lower healthcare resource use and costs compared with matched patients who did not adhere.

One strength of the current study is the approach of linking a therapeutic dataset extracted from the ResMed PAP cloud (Airview^{TM}) with a large administrative database of payor-sourced, adjudicated claims from more than 100 geographically dispersed health plans in the United States, which identified the co-existence of newly diagnosed OSA and COPD (overlap syndrome) in adults, and monitored PAP adherence for 2 years. The authors classified compliance very conservatively, into three categories: nonadherent, adherent and intermediate, if subjects met the standard Center for Medicare and Medicaid Services (CMS) criteria (PAP device usage $\geq$4 hours/night and $\geq$70% of the nights) in none, all, or some of the eight consecutive 90-day periods, respectively. As such, 34% of the 6,810 patients were classified as nonadherent, 26% of the patients were adherent (based on this stringent definition of compliance), and 40% fell into the intermediary category (and they were excluded from analyses). Interestingly, other studies found similar low rates of long-term adherence to PAP therapy in patients with COPD-OSA overlap (9).

Since this was not a RCT, the authors developed a propensity score model based on risk of non-adherence that used logistic regression, which incorporated demographics, comorbidities and prior healthcare utilization, and lead to "targeted" analyses on 712 adherent and 712 non-adherent matched patients. The following covariates were used for group matching: age, gender, payor, obesity, coronary artery disease, heart failure, cerebrovascular disease, type 2 diabetes mellitus, gastroesophageal reflux syndrome, hypertension, anxiety and mood disorders, COPD severity (mild, moderate, or severe), home oxygen therapy, as well as hospitalizations and emergency room visits in the pre-PAP year. Perhaps not unexpectedly, the nonadherent matched group incurred higher average healthcare utilization costs, by $2,734 and $2,417 in the first and second year of follow-up, respectively. In the same time, the sleep-related healthcare costs attributable to sleep apnea equipment in the nonadherent matched subjects were lower by only $583 and $506 in the first and second year of follow-up, respectively. Given that these costs were calculated using the CMS structure of fees, these assessments likely underestimate the "real world" costs incurred by nonadherent overlap patients.

A limitation of the present report is represented by the retrospective observational nature of the study design, which inherently limits the ability to establish causality from the findings. Furthermore, the nature of data collection in an administrative dataset based on claims data limits the ability to determine overall health status, severity of the underlying conditions using more refined, standardized tools, presence of daytime sleepiness, additional lifestyle factors, and patient reported outcome measures that could influence treatment compliance and health outcomes. Another limitation is posed by the exclusion of the intermediary group (40% of the cohort) due to large heterogeneity in PAP usage, which may not reflect "real world" aggregate data.

The growing evidence from observational studies of health benefits from PAP therapy indicates the need for well-designed prospective randomized controlled trials (RCT) or a large and

carefully designed prospective, propensity-matched study of PAP therapy in patients with COPD-OSA overlap. Justification for such studies comes from the inherent limitations and additional questions posed by previous studies, such as the Sleep Apnea cardiovascular Endpoints (SAVE) trial, which indicated limited benefit to cardiovascular outcomes from PAP therapy in patients with moderate/severe OSA, although this study was limited by the exclusion of sleepy patients and by the poor PAP adherence (10). A future trial in COPD-OSA overlap patients should ideally include patients reporting mild/moderate sleepiness, which is a factor associated with increased likelihood of comorbidity and which may impact PAP compliance. The report by Sterling and colleagues should help in the design of such a study, capable to more reliably assess the potential health benefits of PAP therapy in this important patient group. ■

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Coughing Is Not Required to Transmit *Mycobacterium tuberculosis*
Another Nail in the Coffin

For nearly a century, coughing has been deemed central to the transmission of *Mycobacterium tuberculosis* (1). Even as subclinical tuberculosis (TB) has more recently drawn attention as a potential source of transmission (2), it has been argued that the major driver of transmission might be unrelated or unrecognized coughing (3). But even though coughing is the cardinal symptom of TB, its importance in transmission has never been confirmed (4). In 1969, Loudon and Spohn found that nocturnal cough frequency among patients hospitalized with pulmonary TB was not strongly associated with tuberculin status among those patients' household contacts (5). This finding was not revisited until 2018, when Turner and colleagues again found that 24-hour cough frequency was only weakly associated with tuberculin positivity in contacts of individuals with smear-positive TB (6). High *M. tuberculosis* counts in cough aerosols do correlate with infection in contacts (7), but this finding does not

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