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ORIGINAL ARTICLE

Impact of Positive Airway Pressure Therapy Adherence on Outcomes in Patients with Obstructive Sleep Apnea and Chronic Obstructive Pulmonary Disease

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Abstract

Rationale: The co-occurrence of obstructive sleep apnea and chronic obstructive pulmonary disease, termed overlap syndrome, has a poor prognosis. However, data on positive airway pressure (PAP) treatments and their impact on outcomes and costs are lacking.

Objectives: This retrospective observational study investigated the effects of PAP on health outcomes, resource usage, and costs in patients with overlap syndrome.

Methods: Deidentified adjudicated claims data for patients with overlap syndrome in the United States were linked to objectively measured PAP user data. Patients were considered adherent to PAP therapy if they met Centers for Medicare and Medicaid Services criteria for eight 90-day timeframes from device setup through 2-year follow-up. Propensity score matching was used to create comparable groups of adherent and nonadherent patients. Healthcare resource usage was based on the number of doctor visits, all-cause emergency room visits, all-cause hospitalizations, and PAP equipment and supplies, and proxy costs were obtained.

Measurements and Main Results: A total of 6,810 patients were included (mean age, 60.8 yr; 56% female); 2,328 were nonadherent. Compared with the year before therapy, there were significant reductions in the number of emergency room visits, hospitalizations, and severe acute exacerbations during 2 years of PAP therapy in patients who were versus were not adherent (all $P < 0.001$). This improvement in health status was paralleled by a significant reduction in the associated healthcare costs.

Conclusions: PAP usage by patients with overlap syndrome was associated with reduced all-cause hospitalizations and emergency room visits, severe acute exacerbations, and healthcare costs.

Keywords: obstructive sleep apnea; overlap syndrome; health outcomes; costs; PAP therapy

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At a Glance Commentary

Scientific Knowledge on the Subject: Overlap syndrome is associated with a worse prognosis and higher rates of healthcare usage and costs than chronic obstructive pulmonary disease alone. One small study showed that treatment with positive airway pressure (PAP) in patients with overlap syndrome reduced chronic obstructive pulmonary disease–related hospitalization rates, but there is a lack of data on the impact of PAP treatments on health outcomes and costs in patients with overlap syndrome.

What This Study Adds to the Field: By linking a large claims database with PAP usage provided by remote monitoring, this study showed that patients with overlap syndrome who were adherent to PAP therapy had significantly better health outcomes as measured by significantly lower healthcare resource usage and costs than matched patients who did not adhere to PAP therapy. Calculated numbers needed to treat to avoid one healthcare encounter ranged from 1.0 to 18.5, depending on the type of healthcare system encounter.

Obstructive sleep apnea (OSA) is a common condition estimated to affect up to 1 billion people worldwide (1). OSA has important neurocognitive and cardiovascular sequelae, which are at least partially ameliorated by therapeutic interventions (2–4). Chronic obstructive pulmonary disease (COPD) is also common and increasing in prevalence because of exposures including nonsmoking risk factors such as air pollution (5–8). Current therapeutic strategies for COPD are limited, although bronchodilators provide symptomatic relief (5, 9, 10) and may prevent exacerbations when given together with inhaled corticosteroids.

The co-occurrence of OSA and COPD is referred to as overlap syndrome, which is associated with a higher burden of comorbidities than either condition alone and a poor prognosis (11, 12). However, the treatment of overlap syndrome has not been well studied, and the need for additional data has been emphasized (13).

There has been debate about whether COPD is a risk factor for OSA because existing data are largely from patients with mild COPD (8), and some studies have not found a higher rate of patients with sleep apnea with versus without obstructive airway disease (14, 15). In contrast, 67% of a group of patients with moderate to severe COPD referred for pulmonary rehabilitation were found to have OSA on polysomnography in one study (6).

Mechanisms underlying OSA in patients with COPD have been studied, showing similar pathogenesis in individuals with or without COPD (16, 17). However, these findings will likely vary depending on the COPD phenotype (e.g., chronic bronchitis vs. emphysema). Observational study data indicate that survival rates in untreated patients with overlap syndrome are poor compared with those receiving treatment or who have COPD alone (18, 19). Treatment with continuous positive airway pressure (CPAP) not only improved survival but also decreased hospitalizations for COPD exacerbations (18, 19). A *post hoc* analysis of an outpatient database also showed that the use of CPAP reduced mortality in patients with overlap syndrome (20, 21).

We and others have retrospectively analyzed big data or real-world data to investigate patterns of positive airway pressure (PAP) usage in various sleep-related breathing disorders and geographic areas (22–25). These data have provided important insights, but many of these studies have lacked data on important health outcomes. Although patients with overlap syndrome have been shown to have higher healthcare usage and costs than those with COPD alone (26–30), the economic burden of overlap syndrome has not been evaluated with respect to PAP therapy adherence.

This study investigated whether usage of PAP therapy would be associated with improved health outcomes and costs in patients with overlap syndrome compared with similar patients who were nonadherent to PAP treatment on the basis of Centers for Medicare and Medicaid Services (CMS) compliance criteria over a 2-year time period.

Methods

Study Design

This retrospective observational study used deidentified payer-sourced ("closed") adjudicated claims data from more than 100 geographically dispersed health plans in the United States (Inovalon Insights, LLC) and linked these to objective PAP user data from AirView (ResMed). The databases were linked through a tokenized process, and the resulting matched database underwent a Health Insurance Portability and Accountability Act expert evaluation to ensure Health Insurance Portability and Accountability Act compliance. The study design was reviewed by an institutional review board (Advarra, reference number Pro0004005) and deemed exempt from institutional review board oversight.

Study Population

The study cohort included adults (aged $\geq$ 18 yr) who had a new diagnosis of OSA between January 2014 and April 2018. OSA (International Classification of Diseases-10-Clinical Modification G47.33) was diagnosed within 60 days of a sleep test (Healthcare Common Procedure Coding System 95808, 95810, 95811, and G0398-G0400). All patients received PAP therapy using an AirSense 10 PAP device (ResMed Corp) with 1 or more years of claims data before the first sleep test and 2 years of claims data after device setup. COPD was identified by the presence of at least two claim dates with a diagnosis of COPD (J41–44) before PAP device setup and at least two claims for COPD medications or at least one hospitalization or two emergency room (ER) visits related to COPD in the year before device setup. Patients were excluded if the year before PAP device setup included CPAP resupply, a diagnosis of central sleep apnea (G47.31 and G47.37), nocturnal hypoventilation (G47.36), pregnancy (O00.*-O9A.*), end-stage renal disease (N18.6), or dialysis use (Z99.2).

Patient subgroups on the basis of PAP adherence were defined by applying CMS criteria to AirView data. CMS criteria define a patient as adherent if there is PAP device usage for $\geq$4 h/night on $\geq$70% of nights in a 30-day period within a 90-day timeframe. A patient was considered to be adherent if they met CMS criteria for eight consecutive 90-day timeframes from device setup. If

CMS criteria were met in none of the eight consecutive 90-day timeframes, the patient was considered to be nonadherent. Cases in which criteria were met in some but not all timeframes were considered intermediate and excluded from analyses because of the marked heterogeneity of PAP usage in this group (the number of quarters in which patients met CMS adherence criteria ranged between one and seven).

Outcomes and Covariates

Healthcare resource usage was determined on the basis of the number of doctor (physician and hospital) visits, all-cause ER visits, all-cause inpatient hospitalizations, and PAP equipment and supplies (from claims data). Proxy costs for all resource use were provided by Inovalon Insights, LLC, on the basis of their proprietary Proxy Financials algorithm. This algorithm is based on CMS Medicare prospective payment system fee schedules. The approach enriches the dataset with relative amounts that reflect Medicare-allowed payments across provider services and treatments. Adjustments to the standard methodology are made to accommodate relative charge comparisons across patients on the basis of their characteristics. Risk-adjusted models were used to determine the impact of 2-year PAP adherence on the number of all-cause inpatient hospitalizations, all-cause ER visits, and severe acute exacerbations. Severe acute exacerbations included the number of respiratory-related hospitalizations and COPD-related ER visits adapted from Mapel and colleagues (31).

The following covariates were identified and used for risk-adjusted analyses and patient matching: demographic factors (age, payer, sex, and obesity); comorbidities in the year before PAP setup (coronary artery disease, heart failure, cerebrovascular disease, anxiety, depression, psychotic mood disorders, other mood disorders, type 2 diabetes, gastroesophageal reflux disease, and hypertension); COPD complexity in the prior year (low, moderate, and high, as a proxy of disease severity on the basis of the Mapel and colleagues algorithm [31]); and prior year's healthcare resource usage (any usage of home oxygen, all-cause inpatient hospitalization, respiratory inpatient hospitalization, and all-cause ER visits). Medication usage was evaluated in the 90 days before initiation of PAP therapy.

Statistical Analysis

Baseline characteristics are presented using descriptive statistics. A model was created to determine the expected mean number of 2-year all-cause hospitalizations, all-cause ER visits, and severe acute exacerbations using a generalized linear model. Model goodness of fit was assessed by Log-likelihood R-squared (LL-R^2) and 90th percentile predicted range. The number needed to treat (NNT) to avoid an event (e.g., ER visit or hospitalization) was calculated as 1/absolute risk reduction. This was used to quantify the impact of adherence to PAP therapy for the overall population and by risk quartiles (four groups, each reflecting approximately 25% of the study population in increasing risk). NNT represents the number of nonadherent patients that would need to be adherent to PAP therapy to avoid an ER visit, hospitalization, or severe exacerbation.

A propensity score model (32) based on the risk of not adhering was developed using logistic regression and incorporating baseline demographics, comorbidities, and prior healthcare usage. A propensity score was calculated on the basis of model coefficients and used in matching. The receiver operating characteristic area under the curve was calculated to determine how well patient characteristics were able to predict adherence. Adherent and nonadherent groups were precisely matched on the following baseline characteristics: age group, sex, payer type, prior all-cause hospitalizations, and prior all-cause ER visits; other parameters were matched using a propensity score. Then, to ensure the matched cohorts resembled the original nonadherent cohort, adherent patients were matched to a randomly downsampled subgroup of nonadherent patients without replacement. Differences in healthcare resource usage before and after PAP setup and between matched samples were assessed using paired Wilcoxon tests. A sensitivity analysis was conducted using the inverse probability of treatment weighting. Statistical analyses were performed using the *R* statistical package (33, 34) and Python (35).

Results

Study Population

A total of 6,810 patients with overlap syndrome were identified for analysis (mean age, 59.8 yr, 56% female), 2,328 of whom were classified as nonadherent. CMS 90-day compliance rate for the population was 58.1%. Patients were evenly distributed across payer types (Table 1). COPD complexity was low in 27% of patients, moderate in 55%, and high in 18%. Baseline characteristics of the matched population were well matched between the adherent and nonadherent patient cohorts (Table 1). The demographic and clinical characteristics of the intermediate group were similar to those of the adherent and nonadherent groups (*see* Table E1 in the online supplement). Medication use in the 90 days before starting PAP therapy was similar in the adherent and nonadherent matched cohorts (Table E2).

PAP Therapy Usage

PAP usage during the first year of therapy was evaluated in the adherent and nonadherent (unadjusted risk) populations. Patients who adhered to PAP therapy used the device almost every day of the week (median, 6.9 d/wk) and consistently for 7 hours each day on the basis of both median hours per day or hours per use-day (6.9 and 7.2, respectively). In contrast, nonadherent patients used their PAP devices infrequently (median, 0.4 d/wk) and for a short period of time on days when the device was used (median, 0.2 h/d and 2.8 h/use-day).

Risk-adjusted Outcomes

The "number of 2-year all-cause hospitalization model" had a good fit, with an LL-R^2 of 92.5%. The 90th percentile predicted range for the number of all-cause hospitalizations was 0.15–2.07 (median, 0.39). Being adherent to PAP significantly reduced the number of all-cause hospitalizations ($P < 0.0001$), resulting in the avoidance of one hospitalization for every 1.8 adherent patients on average (95% confidence interval [CI], 1.6–2). The magnitude of benefit varied by patient health state, from an NNT of 6.4 in the lowest risk quartile to one hospitalization avoided for every adherent patient in the highest risk quartile.

The "2-year ER model" also fit well, with an LL-R^2 of 97.1%. The 90th percentile range for the number of ER visits per patient every 2 years was 0.91–9.19 (median, 1.80). Being adherent to PAP was significantly associated with a reduced number of ER visits ($P < 0.0001$), avoiding an average of 2.2 ER visits per adherent patient (NNT = 0.46; 95% CI, 0.44–0.49). As for hospitalizations, this estimate varied on the basis of patient health state, from one ER visit avoided for

Table 1. Patient Demographic and Clinical Characteristics at Baseline

Characteristics	All (*N* = 6,810)	Matched Cohort		SMD
		Adherent (*n* = 712)	Nonadherent (*n* = 712)	
Female, *n* (%)	3,792 (55.7)	415 (58.3)	415 (58.3)	0.00
Age, yr	59.8 ± 10.6 (59)	60.2 ± 10.5 (59)	59.9 ± 11.2 (59)	0.03
Age group, *n* (%)				
18–54 yr	2,036 (29.9)	218 (30.6)	218 (30.6)	0.00
55–69 yr	3,512 (51.6)	357 (50.1)	357 (50.1)	0.00
⩾70 yr	1,262 (18.5)	137 (19.2)	137 (19.2)	0.00
Payer, *n* (%)				
Commercial	2,253 (33.1)	168 (23.6)	168 (23.6)	0.00
Medicare Advantage	2,052 (30.1)	233 (32.7)	233 (32.7)	0.00
Medicaid	2,505 (36.8)	311 (43.7)	311 (43.7)	0.00
Obesity, *n* (%)				
Morbidly obese	2,643 (38.8)	285 (40.0)	247 (34.7)	0.11
Obese	1,969 (28.9)	212 (29.8)	223 (31.3)	0.03
No listed obesity	2,198 (32.3)	6,313 (30.2)	6,340 (34.0)	0.08
Home oxygen use, *n* (%)	1,783 (26.2)	190 (26.7)	171 (24.0)	0.06
Tobacco use, *n* (%)	3,205 (47.1)	316 (44.4)	369 (51.8)	0.15
Comorbidities, *n* (%)				
Coronary artery disease	2,487 (36.5)	261 (36.7)	275 (38.6)	0.04
Heart failure	1,918 (28.2)	204 (28.7)	219 (30.8)	0.05
Cerebrovascular disease	842 (12.4)	86 (12.1)	88 (12.4)	0.01
Asthma	3,207 (47.1)	339 (47.6)	336 (47.2)	0.01
Pneumonia	1,536 (22.6)	196 (27.5)	160 (22.5)	0.12
Depression	1,718 (25.2)	198 (27.8)	177 (24.9)	0.07
Anxiety	651 (9.6)	59 (8.3)	62 (8.7)	0.02
Psychotic disorders	775 (11.4)	57 (8.0)	98 (13.8)	0.19
Other mood disorders	468 (6.9)	45 (6.3)	53 (7.4)	0.04
Type 2 diabetes	3,073 (45.1)	327 (45.9)	344 (48.3)	0.05
Hypertension	5,643 (82.9)	594 (83.4)	591 (83.0)	0.01
Gastroesophageal reflux disease	3,248 (47.7)	329 (46.2)	328 (46.1)	0.00

Definition of abbreviation: SMD = standardized mean difference.
Values are mean ± SD (median) or the number of patients (%).

every two adherent patients for those in the lowest risk quartile to three ER visits avoided for every adherent patient in the highest risk quartile.

The "number of 2-year severe acute exacerbation model" fit well with an LL-R^2 of 92.6%. The 90th percentile predicted range for the number of severe acute exacerbations was 0.05–1.06 (median, 0.21). Being adherent to PAP was significantly associated with a reduced number of severe acute exacerbations ($P < 0.0001$), on average avoiding one acute exacerbation for every 4.1 adherent patients (95% CI, 3.6–4.8). The magnitude of benefit again varied by patient health state, from an NNT of 18.5 in the lowest risk quartile to 2.3 exacerbations avoided for every adherent patient in the highest risk quartile.

Figure 1 shows the predicted impact of adherence on the number of all-cause hospitalizations, all-cause ER visits, and severe acute exacerbations. The prediction models demonstrated a broad range of risk for healthcare resource usage (risk score) in patients with overlap syndrome for all three models and across the risk range, with adherent patients having a lower risk for healthcare resource usage than nonadherent patients. In addition to adherence, predictors of healthcare resource usage include resource usage in the prior year, having Medicaid insurance coverage, a high comorbidity burden, and COPD complexity (moderate and high).

Lastly, the "risk of not adhering model" fit well, with an LL-R^2 of 96.7% (Figure E1), and the receiver operating characteristic area under the curve was 0.7198. The 90th percentile range for risk of nonadherence was 28–87% (median, 54%). Covariates associated with a greater risk of not adhering included age of less than 55 years, having Medicaid insurance coverage, mood disorders (of which psychotic disorders were associated with the highest nonadherence risk), and not using home oxygen.

Healthcare Resource Usage and Costs

Table 2 provides a comparison of healthcare resource usage for the matched adherent and nonadherent patients for the year prior and Year 1 and Year 2 after PAP therapy initiation.

There were significant differences between adherent and nonadherent patients in the number of ER visits and inpatient hospitalizations in Year 1 and Year 2 of PAP usage (Table 2 and Figure 2). Reductions in healthcare resource usage in Year 1 continued in Year 2. Significant differences were also observed when comparing costs (total, ER, and inpatient hospitalizations) between adherent and nonadherent patients (Table 3). Costs declined in Year 1 of PAP usage in adherent patients and continued to decrease in Year 2. Hospitalization costs in the adherent patient group decreased over the 2-year period but increased in nonadherent patients. Results from the inverse probability of treatment weighting sensitivity analysis were consistent, showing increased hospitalizations, ER visits, and costs for nonadherent patients (Tables E3–E5).

Sleep-related Costs

Sleep test costs in the year before PAP were similar in adherent and nonadherent patients

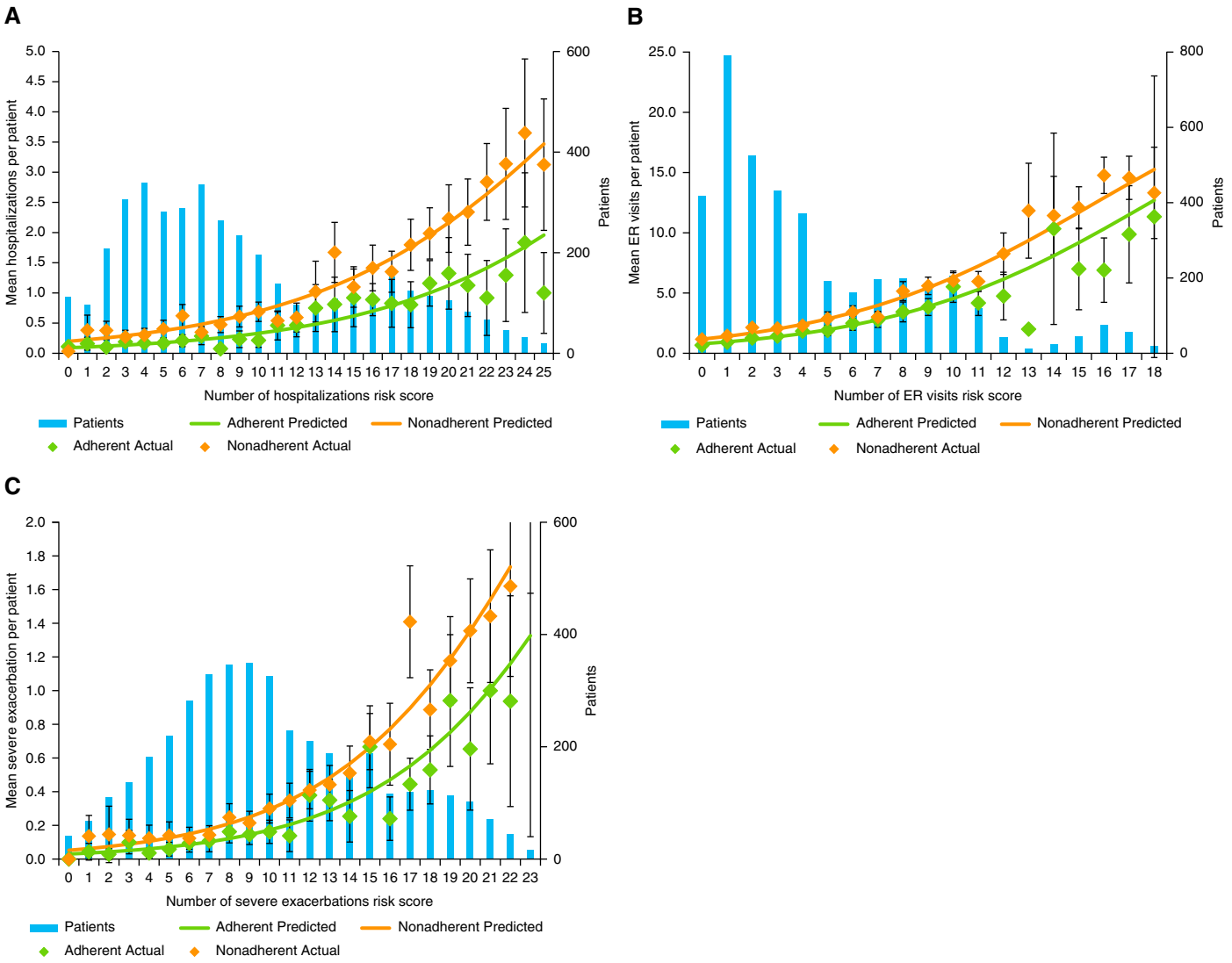

Figure 1. Impact of positive airway pressure therapy adherence on the number of (*A*) all-cause hospitalizations, (*B*) all-cause ER visits, and (*C*) severe exacerbations. Green and yellow solid lines represent values predicted by the risk model. Blue vertical bars represent the number of patients in each risk group. Diamonds represent the actual mean values from the observed data, with error bars representing the 90% confidence intervals. ER = emergency room.

(Table 4). Adherent patients had higher PAP equipment costs than nonadherent patients during both years of therapy, reflecting the use of supplies and PAP device rental fees. Sleep-related healthcare costs (in U.S. dollars) in the adherent patient group ($3,108 ± $1,218) were more than offset by reductions in healthcare costs over 2 years ($6,239).

Discussion

The findings of this retrospective study demonstrated an important reduction in the risk of ER visits and hospitalizations in patients with overlap syndrome who were adherent versus nonadherent with PAP therapy. This improvement in health status was paralleled by a reduction in healthcare costs. On the basis of the absolute risk reductions observed, the calculated NNT values were favorable, providing evidence that treatment of overlap syndrome with PAP therapy is beneficial when adherence to therapy is maintained. These findings add to currently available evidence (18, 20) and may have a potential impact on COPD management.

Singh and colleagues studied a Medicare COPD population with coexisting OSA and reported similar rates of comorbidities (e.g., hypertension, type 2 diabetes, and heart failure) and distribution of COPD complexity (a claims-based proxy for disease severity) to our study (36). Similarly, the distribution of COPD complexity in the current study is consistent with the Medicare COPD and overlap syndrome populations in the study by Starr and colleagues (37). In contrast, Mapel and colleagues studied a population with only COPD who had similar age and sex distribution to our study population but a lower proportion of patients with moderate or high COPD complexity and lower comorbidity rates (31, 38, 39).

To our knowledge, the current study represents the largest to date evaluating the

Table 2. Resource Usage in Unmatched and Matched Cohorts

Resource Usage (Mean Number per Patient)	Unmatched		Matched		
	Adherent (*n* = *1,744*)	Nonadherent (*n* = *2,328*)	Adherent (*n* = *712*)	Nonadherent (*n* = *712*)	*P* Value
Year before PAP					
Doctor visits	14.02	18.48	15.80	17.65	0.01
Emergency room visits	1.27	2.46	1.75	1.89	0.59
Inpatient hospitalizations	0.43	0.54	0.51	0.50	0.67
PAP Year 1					
Doctor visits	14.46	18.04	16.71	17.37	0.33
Emergency room visits	0.94	2.21	1.25	1.83	<0.001
Inpatient hospitalization	0.22	0.49	0.24	0.46	<0.001
PAP Year 2					
Doctor visits	13.37	16.36	15.43	15.71	0.37
Emergency room visits	0.86	2.09	1.16	1.70	<0.001
Inpatient hospitalizations	0.18	0.50	0.21	0.42	<0.001

Definition of abbreviation: PAP = positive airway pressure.

impact of PAP therapy on overlap syndrome. Overlap syndrome was first described in the 1980s, and it was suggested that these individuals were at high risk, although therapeutic studies were lacking at the time (11, 40). Subsequently, a number of studies have assessed the impact of PAP therapy on COPD, but many either overlooked or excluded potential concomitant sleep apnea (41). Köhnlein and colleagues (42) published a randomized trial showing a mortality benefit in patients with hypercapnic COPD treated with bilevel PAP therapy compared with usual care. However, sleep studies were not systematically conducted in that study, and therefore, the potential benefits of treating COPD versus treating overlap syndrome versus treating hypercapnic respiratory failure remained unclear. Murphy and colleagues found that treatment with bilevel PAP was effective in preventing exacerbations in patients with COPD (43). However, again, sleep was not systematically assessed, and thus, the benefits of treating overlap syndrome versus COPD are unclear. Our findings confirm the benefits seen in studies by Marin and colleagues (18) and Stanchina and colleagues (20), both of which reported a reduction in mortality associated with PAP treatment for patients with overlap syndrome, and extend the findings to other important outcomes, including hospitalization and ER visits in a nationally representative population. We are not aware of any randomized trials to date that have investigated therapy for overlap syndrome. Thus, additional observational studies may be required before more definitive data are available. Moreover, we hope our new findings help in the design of subsequent rigorous research studies.

The economic impact of overlap syndrome has been previously investigated, primarily comparing costs in patients with overlap syndrome with those with either COPD alone or COPD with other comorbidities. In a cohort of commercially insured patients from the United States, patients with overlap syndrome had significantly higher rates of hospitalization and ER visits and greater medical expenditure (inpatient, ER, pharmacy, physician, and other outpatient services) than those with COPD alone (30, 44). Similarly, the presence of comorbid OSA had associations with higher all-cause hospitalizations, COPD-related hospitalizations, and all-cause healthcare costs in a population from a U.S. national health plan with commercially insured and Medicare Advantage plans (30). The greatest impact of comorbid OSA was seen on COPD-related healthcare costs (30). Furthermore, data from Germany showed that sleep apnea significantly contributed to total direct costs in patients with COPD, including the cost of hospitalizations (45).

Although these studies clarify the additional economic burden on the healthcare system associated with overlap syndrome, they do not address the value of treating these patients with PAP therapy. To our knowledge, there is only one previous study looking at the impact of initiating PAP therapy in an overlap syndrome population. Using a 5% sample of Medicare fee-for-service beneficiaries with COPD, Singh and colleagues identified 319 patients with comorbid OSA (36). They found that COPD-related hospitalization rates were lower after PAP initiation (identified by Healthcare Common Procedure Coding System codes), but other ER visits and all-cause hospitalization rates did not differ in users versus nonusers of PAP therapy (although the sample size limits the ability to draw definitive conclusions) (36).

Reducing COPD exacerbations is an important treatment target. The current study identified a substantial effect of PAP therapy on health outcomes in patients with overlap syndrome, including reducing the rate of severe acute exacerbations. Triple pharmacologic therapy with long-acting muscarinic antagonists and β agonists plus inhaled corticosteroids has been shown to reduce the number of COPD exacerbations by around 25% (46). In addition, noninvasive ventilation therapy has been shown to improve health status in patients with COPD (47).

Key strengths of this study include the sample size and the fact that the findings should have quite good generalizability to the wider overlap syndrome population because of the diversity and geographic distribution of the real-world population. Furthermore, objective measures of PAP adherence were used, and these are applicable to routine clinical practice. However, a number of limitations need to be taken into account when interpreting the findings. First, the data are observational and, therefore, must be considered correlational rather than causal. There are potentially missing covariates from the dataset, such as smoking, alcohol, and other lifestyle factors (e.g., nutrition, physical activity, and sleep duration). However, we conducted a cautious propensity score

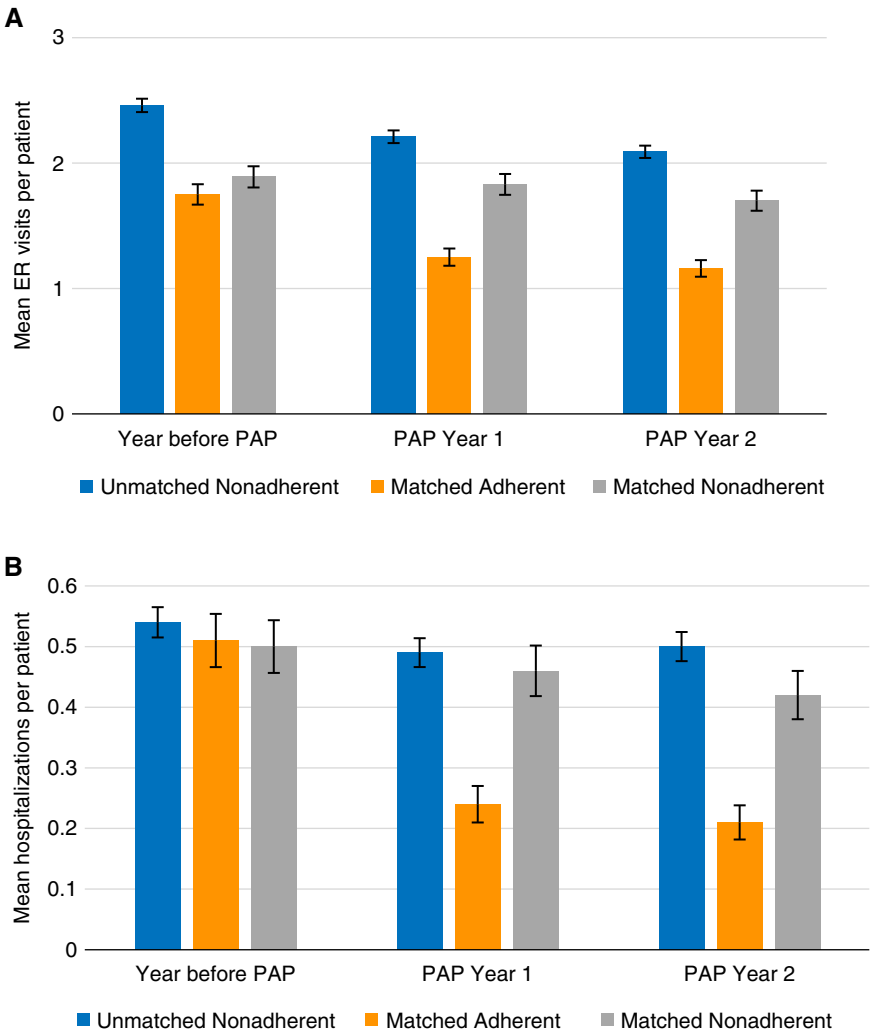

Figure 2. Mean number of (*A*) ER visits and (*B*) hospitalizations in different patient cohorts. Error bars represent 90% confidence intervals. Blue, orange, and gray vertical bars represent the mean number of healthcare resource usage per patient in the cohort. ER = emergency room; PAP = positive airway pressure.

matching to try and improve the reliability of our findings (48). Nevertheless, large-scale randomized trials would be helpful in extending the findings of this study.

Second, although we had access to a U.S. nationally representative matched dataset with a large number of commercially insured patients with Medicaid and Medicare Advantage, the claims dataset did not contain patients with Medicare fee-for-service and therefore had limited generalizability to this patient population. In addition, the sample included slightly more females than males, which may be driven by the use of a data source with a large proportion of Medicaid recipients, many of whom are female. Although analysis of the demographic makeup of the claims dataset revealed similarities to the U.S. population reported by the U.S. Census Bureau, there remains the possibility of unknown biases based on the health plans that contribute to the database. We, therefore, support further efforts to enrich datasets with patients who fully represent the broad diversity of the populations of interest. Moreover, we would welcome efforts to identify subsets of patients with overlap syndrome who may be particularly amenable to interventions.

Third, the outcome measures studied were limited by the available claims data and thus may not reflect the overall health of participants. For example, we do not have laboratory data or patient-reported outcomes, which may be motivating factors for many patients. However, data on clinically relevant hard clinical outcomes are reported, which we believe will complement subsequent studies with additional outcome assessments.

Fourth, our study used a conservative definition of adherence on the basis of attaining CMS compliance in all eight quarters over a 2-year period using objective PAP therapy usage data to compare a treated cohort with an untreated cohort. Thus, our findings may not apply to patients with sporadic PAP usage. Further research is needed to understand the dose–response relationship between PAP usage and outcomes to better account for patients who fall between our definitions of adherent and nonadherent, as well as to assess the influence of hospitalizations on subsequent adherence.

Finally, the reliance on comparisons between adherent and nonadherent patients, and therefore the current findings, may be subject to the healthy user effect. That is, adherence to PAP therapy may be indicative of better education, socioeconomic status, health literacy, or other social determinants of health. Of note, propensity matching was performed to ensure that the groups compared were similar in terms of age, sex, comorbidities, insurance coverage, and other factors, but the possibility of some residual confounding cannot be excluded. Thus, randomized trials are an important next step (although the healthy user effect can still be observed in the context of randomized trials).

Conclusions

This real-world data study showed that PAP usage by patients with overlap syndrome was associated with reduced all-cause hospitalizations, all-cause ER visits, severe acute exacerbations, and healthcare costs. This finding has important implications for clinical screening of patients with COPD for overlap syndrome, prescription of PAP, and ensuring patients remain adherent to PAP therapy. ■

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Table 3. Healthcare Resource Costs in Unmatched and Matched Cohorts

Costs* (U.S. Dollars)	Unmatched		Matched		
	Adherent (*n* = *1,744*)	Nonadherent (*n* = *2,328*)	Adherent (*n* = *712*)	Nonadherent (*n* = *712*)	*P* Value
Year before PAP					
Total	13,161 ± 15,414	15,447 ± 16,778	14,550 ± 17,650	14,283 ± 15,863	0.98
Doctor visits	2,387 ± 2,640	2,682 ± 2,876	2,378 ± 2,282	2,602 ± 2,605	0.10
Emergency room visits	898 ± 1,811	1,665 ± 3,162	1,183 ± 2,342	1,217 ± 2,805	0.76
Inpatient hospitalizations	5,069 ± 13,261	5,962 ± 13,959	5,839 ± 15,475	5,523 ± 12,869	0.76
PAP Year 1					
Total	10,570 ± 11,761	14,538 ± 19,074	11,132 ± 11,562	13,866 ± 19,442	0.03
Doctor visits	2,195 ± 2,033	2,523 ± 2,863	2,350 ± 2,184	2,398 ± 2,335	0.49
Emergency room visits	693 ± 1,683	1,490 ± 2,754	914 ± 2,238	1,221 ± 2,480	<0.001
Inpatient hospitalizations	2,442 ± 8,434	5,665 ± 15,595	2,473 ± 8,131	5,160 ± 15,866	<0.001
PAP Year 2					
Total	9,006 ± 12,588	13,470 ± 19,554	9,953 ± 12,678	12,370 ± 18,932	0.06
Doctor visits	2,180 ± 2,554	2,295 ± 2,898	2,322 ± 2,639	2,334 ± 3,008	0.55
Emergency room visits	644 ± 2,197	1,428 ± 2,896	891 ± 3,151	1,187 ± 2,814	<0.001
Inpatient hospitalizations	2,274 ± 9,534	5,728 ± 16,238	2,432 ± 9,589	4,881 ± 15,450	<0.001

Definition of abbreviation: PAP = positive airway pressure.
Values are mean ± SD.
*Proxy costs for all resource usage were provided by Inovalon Insights, LLC, on the basis of their proprietary Proxy Financials Algorithm.

Table 4. Sleep-related Healthcare Resource Costs

Costs* (U.S. Dollars)	Unmatched		Matched		
	Adherent (*n* = *1,744*)	Nonadherent (*n* = *2,328*)	Adherent (*n* = *712*)	Nonadherent (*n* = *712*)	*P* Value
Year before PAP					
Sleep test	1,128 ± 659	1,159 ± 685	1,131 ± 639	1,088 ± 656	0.21
PAP Year 1					
Apnea equipment	1,341 ± 629	720 ± 478	1,347 ± 612	764 ± 488	<0.001
PAP Year 2					
Apnea equipment	584 ± 485	125 ± 323	630 ± 522	124 ± 326	<0.001

Definition of abbreviation: PAP = positive airway pressure
Values are mean ± SD.
*Proxy costs for all resource use were provided by Inovalon Insights, LLC, on the basis of their proprietary Proxy Financials Algorithm.

References

1. Benjafield AV, Ayas NT, Eastwood PR, Heinzer R, Ip MSM, Morrell MJ, *et al.* Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med* 2019;7: 687–698.
2. Jenkinson C, Davies RJ, Mullins R, Stradling JR. Comparison of therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomized prospective parallel trial. *Lancet* 1999;353:2100–2105.
3. Labarca G, Saavedra D, Dreyse J, Jorquera J, Barbe F. Efficacy of CPAP for improvements in sleepiness, cognition, mood, and quality of life in elderly patients with OSA: systematic review and meta-analysis of randomized controlled trials. *Chest* 2020;158:751–764.
4. Labarca G, Schmidt A, Dreyse J, Jorquera J, Enos D, Torres G, *et al.* Efficacy of continuous positive airway pressure (CPAP) in patients with obstructive sleep apnea (OSA) and resistant hypertension (RH): systematic review and meta-analysis. *Sleep Med Rev* 2021;58:101446.
5. Celli BR, Wedzicha JA. Update on clinical aspects of chronic obstructive pulmonary disease. *N Engl J Med* 2019;381:1257–1266.
6. Soler X, Gaio E, Powell FL, Ramsdell JW, Loredo JS, Malhotra A, *et al.* High prevalence of obstructive sleep apnea in patients with moderate to severe chronic obstructive pulmonary disease. *Ann Am Thorac Soc* 2015;12:1219–1225.
7. Budhiraja R, Siddiqi TA, Quan SF. Sleep disorders in chronic obstructive pulmonary disease: etiology, impact, and management. *J Clin Sleep Med* 2015;11:259–270.
8. Sharma B, Feinsilver S, Owens RL, Malhotra A, McSharry D, Karbowitz S. Obstructive airway disease and obstructive sleep apnea: effect of pulmonary function. *Lung* 2011;189:37–41.
9. Brunette AM, Warner K, Holm KE, Meschede K, Wamboldt FS, Kozora E, *et al.* Daily activities: the impact of COPD and cognitive dysfunction. *Arch Clin Neuropsychol* 2021;36:acaa090 767 779–767.
10. Kim V, Zhao H, Regan E, Han MK, Make BJ, Crapo JD, *et al.*; COPDGene Investigators. The St. George's respiratory questionnaire definition of chronic bronchitis may be a better predictor of COPD exacerbations compared with the classic definition. *Chest* 2019;156: 685–695.
11. Flenley DC. Sleep in chronic obstructive lung disease. *Clin Chest Med* 1985;6:651–661.

12. Adler D, Bailly S, Benmerad M, Joyeux-Faure M, Jullian-Desayes I, Soccal PM, *et al.* Clinical presentation and comorbidities of obstructive sleep apnea-COPD overlap syndrome. *PLoS One* 2020;15:e0235331.
13. Malhotra A, Schwartz AR, Schneider H, Owens RL, DeYoung P, Han MK, *et al.*; ATS Assembly on Sleep and Respiratory Neurobiology. Research priorities in pathophysiology for sleep-disordered breathing in patients with chronic obstructive pulmonary disease. An official American Thoracic Society research statement. *Am J Respir Crit Care Med* 2018;197:289–299.
14. Sanders MH, Newman AB, Haggerty CL, Redline S, Lebowitz M, Samet J, *et al.*; Sleep Heart Health Study. Sleep and sleep-disordered breathing in adults with predominantly mild obstructive airway disease. *Am J Respir Crit Care Med* 2003;167:7–14.
15. Zhao YY, Blackwell T, Ensrud KE, Stone KL, Omachi TA, Redline S; Osteoporotic Fractures in Men (MrOS) Study Group. Sleep apnea and obstructive airway disease in older men: outcomes of sleep disorders in older men study. *Sleep* 2016;39:1343–1351.
16. Orr JE, Schmickl CN, Edwards BA, DeYoung PN, Brena R, Sun XS, *et al.* Pathogenesis of obstructive sleep apnea in individuals with the COPD + OSA overlap syndrome versus OSA alone. *Physiol Rep* 2020;8:e14371.
17. Biselli P, Grossman PR, Kirkness JP, Patil SP, Smith PL, Schwartz AR, *et al.* The effect of increased lung volume in chronic obstructive pulmonary disease on upper airway obstruction during sleep. *J Appl Physiol* 2015;119:266–271.
18. Marin JM, Cote CG, Diaz O, Lisboa C, Casanova C, Lopez MV, *et al.* Prognostic assessment in COPD: health related quality of life and the BODE index. *Respir Med* 2011;105:916–921.
19. Marin JM, Soriano JB, Carrizo SJ, Boldova A, Celli BR. Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome. *Am J Respir Crit Care Med* 2010; 182:325–331.
20. Stanchina ML, Welicky LM, Donat W, Lee D, Corrao W, Malhotra A. Impact of CPAP use and age on mortality in patients with combined COPD and obstructive sleep apnea: the overlap syndrome. *J Clin Sleep Med* 2013;9:767–772.
21. Ioachimescu OC, Janocko NJ, Ciavatta MM, Howard M, Warnock MV. Obstructive Lung Sisease and Obstructive Sleep Apnea (OLDOSA) cohort study: 10-year assessment. *J Clin Sleep Med* 2020;16:267–277.
22. Malhotra A, Crocker ME, Willes L, Kelly C, Lynch S, Benjafield AV. Patient engagement using new technology to improve adherence to positive airway pressure therapy: a retrospective analysis. *Chest* 2018; 153:843–850.
23. Cistulli PA, Armitstead J, Pepin JL, Woehrle H, Nunez CM, Benjafield A, *et al.* Short-term CPAP adherence in obstructive sleep apnea: a big data analysis using real world data. *Sleep Med* 2019;59:114–116.
24. Drager LF, Malhotra A, Yan Y, Pepin JL, Armitstead JP, Woehrle H, *et al.*; medXcloud Group. Adherence with positive airway pressure therapy for obstructive sleep apnea in developing versus developed countries: a big data study. *J Clin Sleep Med* 2020;17: 703–709.
25. Pépin JL, Bailly S, Rinder P, Adler D, Szeftel D, Malhotra A, *et al.*; medXcloud Group. CPAP therapy termination rates by osa phenotype: a French nationwide database analysis. *J Clin Med* 2021;10:936.
26. Wacker ME, Jörres RA, Karch A, Koch A, Heinrich J, Karrasch S, *et al.*; COSYCONET study group. Relative impact of COPD and comorbidities on generic health-related quality of life: a pooled analysis of the COSYCONET patient cohort and control subjects from the KORA and SHIP studies. *Respir Res* 2016;17:81.
27. Wacker ME, Jörres RA, Karch A, Wilke S, Heinrich J, Karrasch S, *et al.*; COSYCONET-Consortium. Assessing health-related quality of life in COPD: comparing generic and disease-specific instruments with focus on comorbidities. *BMC Pulm Med* 2016;16:70.
28. Wacker ME, Kitzing K, Jörres RA, Leidl R, Schulz H, Karrasch S, *et al.* The contribution of symptoms and comorbidities to the economic impact of COPD: an analysis of the German COSYCONET cohort. *Int J Chron Obstruct Pulmon Dis* 2017;12:3437–3448.
29. Hong KS, Kim MC, Ahn JH. Sarcopenia is an independent risk factor for NAFLD in COPD: a nationwide survey (KNHANES 2008-2011). *Int J Chron Obstruct Pulmon Dis* 2020;15:1005–1014.
30. Schwab P, Dhamane AD, Hopson SD, Moretz C, Annavarapu S, Burslem K, *et al.* Impact of comorbid conditions in COPD patients on health care resource utilization and costs in a predominantly Medicare population. *Int J Chron Obstruct Pulmon Dis* 2017;12:735–744.
31. Mapel DW, Dutro MP, Marton JP, Woodruff K, Make B. Identifying and characterizing COPD patients in US managed care. A retrospective, cross-sectional analysis of administrative claims data. *BMC Health Serv Res* 2011;11:43.
32. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 2011;46:399–424.
33. Singh Sekhon J, Saarinen T. Matching: multivariate and propensity score matching with balance optimization. The R Foundation; 2022 [accessed 16 Mar 2022]. Available from: https://cran.r-project.org/web/packages/Matching/.
34. Geskus RB, van der Wal W. ipw: estimate inverse probability weights. The R Foundation; 2022 [accessed 16 Mar 2022]. Available from https://cran.r-project.org/web/packages/ipw/.
35. scipy.stats.wilcoxon. The SciPy Community [accessed 11 Aug 2021]. Available from: https://docs.scipy.org/doc/scipy/reference/generated/scipy.stats.wilcoxon.html.
36. Singh G, Agarwal A, Zhang W, Kuo YF, Sultana R, Sharma G. Impact of PAP therapy on hospitalization rates in Medicare beneficiaries with COPD and coexisting OSA. *Sleep Breath* 2019;23:193–200.
37. Starr P, Agarwal A, Singh G, Hsu E, Zhang W, Kuo YF, *et al.* Obstructive sleep apnea with chronic obstructive pulmonary disease among medicare beneficiaries. *Ann Am Thorac Soc* 2019; 16:153–156.
38. Mapel DW, Dalal AA, Johnson P, Becker L, Hunter AG. A clinical study of COPD severity assessment by primary care physicians and their patients compared with spirometry. *Am J Med* 2015;128:629–637.
39. Mapel DW, Dalal AA, Johnson PT, Becker LK, Hunter AG. Application of the new GOLD COPD staging system to a US primary care cohort, with comparison to physician and patient impressions of severity. *Int J Chron Obstruct Pulmon Dis* 2015;10:1477–1486.
40. Flenley DC. Hypoxaemia during sleep. *Thorax* 1980;35:81–84.
41. McEvoy RD, Pierce RJ, Hillman D, Esterman A, Ellis EE, Catcheside PG, *et al.*; Australian trial of non-invasive Ventilation in Chronic Airflow Limitation (AVCAL) Study Group. Nocturnal non-invasive nasal ventilation in stable hypercapnic COPD: a randomised controlled trial. *Thorax* 2009;64:561–566.
42. Köhnlein T, Windisch W, Köhler D, Drabik A, Geiseler J, Hartl S, *et al.* Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. *Lancet Respir Med* 2014;2:698–705.
43. Murphy PB, Rehal S, Arbane G, Bourke S, Calverley PMA, Crook AM, *et al.* Effect of home noninvasive ventilation with oxygen therapy vs oxygen therapy alone on hospital readmission or death after an acute COPD exacerbation: a randomized clinical trial. *JAMA* 2017;317:2177–2186.
44. Hong YD, Onukwugha E, Slejko JF. The economic burden of comorbid obstructive sleep apnea among patients with chronic obstructive pulmonary disease. *J Manag Care Spec Pharm* 2020; 26:1353–1362.
45. Wacker ME, Jörres RA, Schulz H, Heinrich J, Karrasch S, Karch A, *et al.*; COSYCONET-Consortium. Direct and indirect costs of COPD and its comorbidities: results from the German COSYCONET study. *Respir Med* 2016;111:39–46.
46. Rabe KF, Martinez FJ, Ferguson GT, Wang C, Singh D, Wedzicha JA, *et al.*; ETHOS Investigators. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD. *N Engl J Med* 2020;383: 35–48.
47. Meecham Jones DJ, Paul EA, Grahame-Clarke C, Wedzicha JA. Nasal ventilation in acute exacerbations of chronic obstructive pulmonary disease: effect of ventilator mode on arterial blood gas tensions. *Thorax* 1994;49:1222–1224.
48. Pack AI, Magalang UJ, Singh B, Kuna ST, Keenan BT, Maislin G. To RCT or not to RCT? Depends on the question. A response to McEvoy et al. *Sleep* 2021;44:zsab042.