CHEST

Association Between Healthy Behaviors and Health Care Resource Use With Subsequent Positive Airway Pressure Therapy Adherence in OSA

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BACKGROUND: The healthy adherer effect has gained increasing attention as a potential source of bias in observational studies examining the association of positive airway pressure (PAP) adherence with health outcomes in OSA.

RESEARCH QUESTION: Is adherence to PAP associated with healthy behaviors and health care resource use prior to device prescription?

STUDY DESIGN AND METHODS: Data from the Institut de Recherche en Santé Respiratoire (IRSR) des Pays de la Loire Sleep Cohort were linked to health administrative data to identify proxies of heathy behaviors, including adherence to cardiovascular (CV) drugs (medical possession ratio), cancer screening tests, influenza vaccination, alcohol and smoking consumption, and drowsiness-related road accidents during the 2 years preceding PAP onset in patients with OSA. Multivariable regression analyses were conducted to evaluate the association of heathy behaviors with subsequent PAP adherence. Health care resource use was evaluated according to subsequent PAP adherence.

RESULTS: We included 2,836 patients who had started PAP therapy between 2012 and 2018 (65% of whom were PAP adherent with mean daily use $\geq$ 4 h/night). Being adherent to CV active drugs (medical possession ratio $\geq$ 80%) and being a person who does not smoke were associated with a higher likelihood of PAP adherence (OR, 1.43; 95% CI, 1.15-1.77 and OR, 1.37; 95% CI, 1.10-1.71, respectively). Patients with no history of drowsiness-related road accidents were more likely to continue PAP (OR, 1.39; 95% CI, 1.04-1.87). Patients who were PAP adherent used less health care resources 2 years before PAP initiation than patients who were nonadherent (mean number of outpatient consultations: 19.0 vs 17.2, $P = .003$; hospitalization days: 5.7 vs 5.0; $P = .04$; ED visits: 30.7% vs 24.0%, $P = .0002$, respectively).

INTERPRETATION: This study indicated that patients who adhere to PAP therapy for OSA were more health-seeking and used less health care resources prior to device initiation than patients who were nonadherent. Until the healthy adherer effect associated with PAP adherence is better understood, caution is warranted when interpreting the association of PAP adherence with CV health outcomes and health care resource use in nonrandomized cohorts.

CHEST 2024; 166(4):845-856

KEY WORDS: adherence; healthy adherer effect; healthy behaviors; health care resource use; OSA; positive airway pressure

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ABBREVIATIONS: AHI = apnea hypopnea index; CV = cardiovascular; HAE = healthy adherer effect; IRSR = Institut de Recherche en Santé Respiratoire; MPR = medication possession ratio; PAP = positive airway pressure; PSA = prostate-specific antigen; PSG = polysomnography; RCT = randomized controlled trial; SNDS = Système National des Données de Santé

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Take-home Points

Study Question: Is adherence to positive airway pressure (PAP) therapy for OSA associated with healthy behaviors and health care resource use prior to device prescription?

Results: Compared with patients who were nonadherent, those who adhere to PAP therapy were more likely to adhere to cardiovascular active drug use and to not smoke, were less likely to report drowsiness-related road accidents, and used less health care resources prior to device initiation.

Interpretation: These findings support the hypothesis of healthy behaviors associated with adherence to PAP therapy. Further work is needed to identify a study design that could be used to minimize the healthy adherer effect when examining the association of PAP adherence with health outcomes in observational studies.

OSA is thought to affect up to 1 billion people worldwide.[1] Evidence suggests that OSA is an important contributor to poor health outcomes, including neurocognitive impairment, cardiovascular (CV) disease, early mortality, and health care costs.[2,3]

The preventive effect of positive airway pressure (PAP) therapy of moderate-to-severe OSA on CV morbidity and mortality remains uncertain. Indeed, randomized controlled trials (RCTs) treating OSA with PAP have failed to demonstrate improvements in long-term secondary CV disease risk reduction.[4-6] However, limitations in these trials could explain the negative results. Because of ethical concerns about randomizing patients with excessive daytime sleepiness, these trials were performed in patients with OSA with levels of sleepiness considerably lower than typically seen in clinical practice and consequently poorer adherence to PAP, which precludes the generalization of their data to clinical samples.[7] Real-world data represent a potentially promising method for overcoming the sample selection biases described in RCTs of CV end points in OSA. Large observational studies report that patients with OSA who refuse or do not adhere to PAP therapy experience higher rates of CV morbidity and mortality than patients who adhere to PAP.[8-11] However, caution is needed when interpreting observational data linking treatment adherence with health outcomes, a widespread mistake being to confuse the concepts of association and causality.[12] The healthy adherer effect (HAE) is a phenomenon in which patients who take their medications as prescribed tend to take better care of themselves by engaging in various healthy behaviors aimed at improving or maintaining health. Because many of these behaviors may not be measured easily and others may not even be known to the investigators, any favorable effect on health outcomes can then be incorrectly attributed to the examined therapy in observational studies. Previous studies have demonstrated that patients who adhere to treatment for chronic disease (eg, lipid-lowering drugs) are more likely to seek out preventive health services (eg, cancer screening tests, vaccinations).[13] Patients who adhere to statins are also less likely than patients who are nonadherent to experience negative health outcomes (eg, motor vehicle accidents), with this finding being unlikely to be related to a therapeutic effect of lipid-lowering drugs.[14] In a meta-analysis of eight RCTs, nonadherence to placebo was associated with a 1.79-fold increase in mortality.[15] Despite an increasing awareness that the HAE is particularly relevant to comparison of health outcomes between patients with OSA who are adherent and those who are nonadherent or less adherent to PAP therapy,[16,17] there has been little effort to study it directly. Few studies have evaluated the association between PAP use and adherence to CV medications, and reported conflicting findings.[18,19]

The aim of this study was to seek evidence of the HAE among patients from a large multicenter clinic-based cohort (IRSR des Pays de la Loire Sleep Cohort) of patients initiating PAP therapy for OSA. We hypothesized

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DOI: https://doi.org/10.1016/j.chest.2024.05.024

that patients who were adherent to PAP therapy during the first 2 years of treatment would be more actively concerned about their health and engaged in healthy behaviors prior to device prescription than patients who were nonadherent. To explore this hypothesis, we examined the association of PAP adherence with a broad spectrum of proxies measured during the 2 years preceding OSA diagnosis and PAP initiation. A secondary objective of our study was to analyze health care resource use before and after PAP initiation, as surrogates of health status according to PAP adherence. We hypothesized that the association between lower health care consumption and greater PAP adherence could predate OSA diagnosis and device prescription.

Study Design and Methods

Study Design and Population

The study relied on data collected by the multicenter longitudinal study IRSR des Pays de la Loire Sleep Cohort, which was further linked with data from the French administrative health care database (Système National des Données de Santé [SNDS], see Gagnadoux et al[20] and Justeau et al[21] for details) (e-Table 1). All patients with newly diagnosed OSA (apnea hypopnea index [AHI] $\geq$ 15 events/h of sleep [or recording] on in-laboratory polysomnography [PSG] or type 3 home sleep apnea testing) who had started PAP treatment between January 1, 2012, and December 31, 2018, and had available SNDS data were considered for inclusion. Patients declining PAP treatment, opting for alternative OSA therapies, or in palliative care were not included. All participants had given written informed consent. This study was approved by the University of Angers ethics committee (Comité d'Ethique du Centre Hospitalier Universitaire d'Angers, No. 2007/17; Comité Consultative sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé, 07.207bis).

Baseline Evaluation

Each patient completed surveys including anthropometric data, medical history, and medications. The diagnosis of OSA was based on type 3 home sleep apnea testing or PSG, according to pretest clinical probability.[22] Respiratory events were scored manually using recommended criteria.[23] Apnea was defined as $\geq$ 90% decrease in the oronasal airflow sensors, and hypopnea was defined as $\geq$ 30% decrease in nasal pressure signal combined with either $\geq$ 3% arterial oxygen desaturation or an arousal (PSG), both lasting at least 10 s.

Adherence to PAP Therapy

As described previously,[20] PAP therapy was prescribed to patients with severe OSA or with mild-to-moderate OSA with CV comorbidities or severe daytime sleepiness. A single home care provider (Asten Sante) was involved in this study for PAP device delivery and follow-up. All patients were treated with devices equipped with a microprocessor and pressure monitor, providing a precise index of daily use by measuring the time spent with the mask on. All patients received treatment education by a specialized nurse, mask-fitting, and a PAP acclimatization period during the daytime. Follow-up by the home care provider included phone calls during the first week of treatment and visits at 3 and 6 months and then semiannually. Based on the digital downloads from PAP devices, objective daily PAP use (average number of daily hours of PAP use since the last visit) was collected at each follow-up visit by the home care provider and documented in the database. The average of all recorded measurements of daily PAP use was then calculated over the 2 years of follow-up. Patients who had not discontinued PAP and used it on average $\geq$ 4 h/night during the 2-year follow-up period were assigned to the PAP adherent group. Patients who stopped the use of PAP or used the device on average $<$ 4 h/night constituted the nonadherent group. PAP therapy termination was defined as the cessation of PAP reimbursement, as triggered by the physician in charge of patient follow-up. The date of PAP termination was recorded in the IRSR des Pays de la Loire Sleep Cohort database, and the definitive cessation of PAP therapy reimbursement was verified in the SNDS database.

Proxies of Healthy Behaviors

Based on previous reports in the field,[13,14] we examined PAP adherence association with a broad spectrum of healthy behavior proxies measured during the 2 years before PAP initiation, including smoking habits, adherence to CV drugs, cancer screening, and influenza vaccinations. We also analyzed the occurrence of drowsiness-related near-missed or car accidents before PAP initiation, assuming that driving with excessive daytime sleepiness represents a risk-seeking behavior (Fig 1).

Adherence to CV drugs (beta blockers, platelet aggregation inhibitors, antihypertensive drugs, and lipid-modifying agents) was assessed from the SNDS database during the 2 years preceding PAP initiation, using the

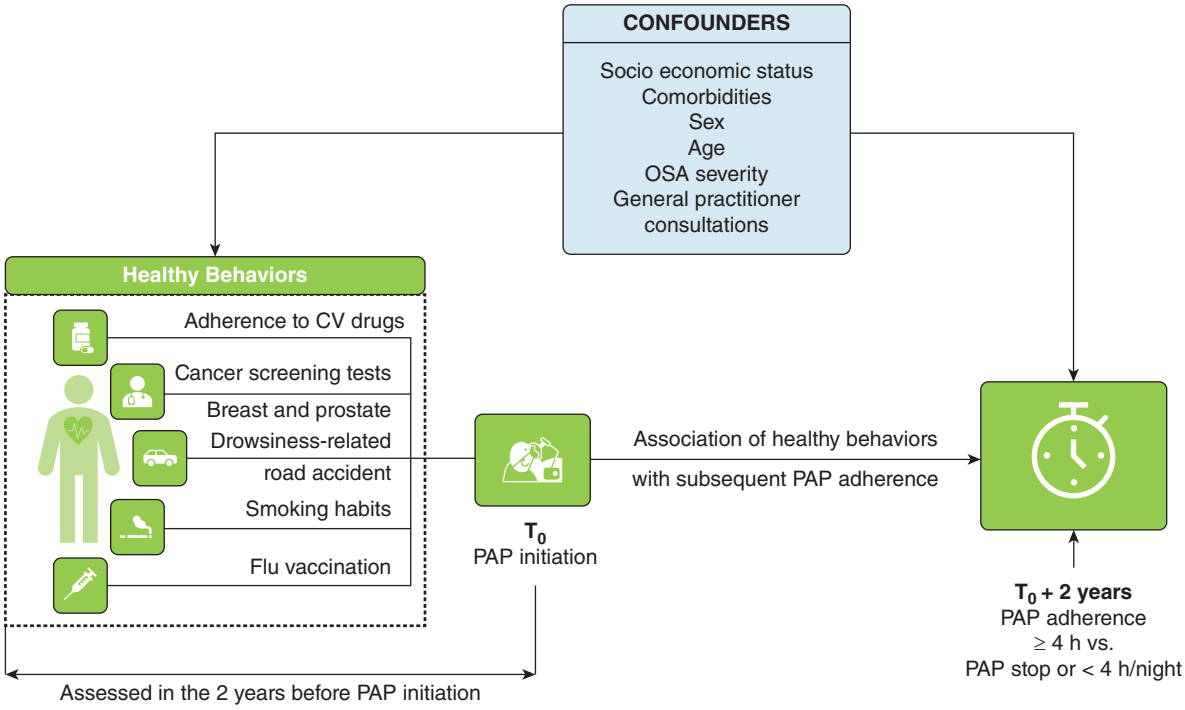

Figure 1 – *Study design and methodology. CV = cardiovascular; PAP = positive airway pressure.*

medication possession ratio (MPR), which corresponds to the number of days of treatment delivered divided by the number of days of follow-up. For each CV active drug, patients who had at least one delivery in the 2 years preceding PAP onset were included in the calculation of MPR and the analysis of its association with subsequent PAP adherence. Patients with an MPR ≥ 80% were considered as treatment adherent.[24,25]

Cancer screening tests collected from the SNDS database during the 2 years preceding PAP initiation included mammography for women aged 50 to 74 years and prostate-specific antigen (PSA) testing for men in the same age range. In France, as part of organized screenings for breast cancer, women aged 50 to 74 years receive biennial invitations to perform a free mammography. For prostate cancer, clinicians decide to perform PSA tests depending on patient's choice, general health, and life expectancy. The study populations for cancer screening tests were women aged 50 to 74 years for mammography and men of the same age for PSA tests. Annual influenza vaccination is recommended for adults aged ≥ 65 years, adults with chronic disease, adults with BMI ≥ 40 kg/m^2, or pregnant women. Taking into account the data available in the IRSR des Pays de la Loire Sleep Cohort and SNDS databases, the study population for influenza vaccination included patients aged ≥ 65 years; those with BMI ≥ 40 kg/m^2; and those with medical history of chronic heart failure, COPD, stroke, coronary heart disease, and/or diabetes. Previous history of car accidents was investigated at inclusion by the following question: Have you ever nodded off or fallen asleep while driving over the past 2 years?

Health Care Resources Use

Health care resources utilization was assessed 2 years before and 2 years after PAP therapy initiation through the number of outpatient consultations, general practitioner consultations, outpatient consultations in hospital, days of hospitalization, and percentage of patients with at least one ED visit during the analyzed period.

Statistical Analysis

Data were described as number and percentage for qualitative variables and median and interquartile range for continuous variables. Patients were compared regarding PAP adherence group by using nonparametric Mann-Whitney *U* test for quantitative variables and χ^2 test for qualitative variables.

Missing values were considered at random and were imputed by using the multiple imputation chained equation method.[26] Five imputed data sets were constituted and merged to assess the results for each model.

A mixed logistic regression model was conducted with a random effect on center to evaluate the association

between proxies of healthy behaviors and subsequent PAP adherence. The following major confounding variables[12] were entered in the model: age, sex, BMI, tobacco consumption, AHI, diabetes, depression, hypertension, history of CV diseases, number of general practitioner consultations, marital status, and educational level. For each healthy behaviors proxy (adherence to CV active drugs, cancer screening tests, influenza vaccination), the multivariable analysis of its association with subsequent PAP adherence was restricted to the subgroup of patients concerned by this treatment or preventive measure. Comparison of health care resource utilization before and after PAP initiation for adherent and nonadherent patient groups was performed using the Wilcoxon signed-rank nonparametric test for paired values. A threshold *P* value of .05 was considered significant. Statistical analyses were performed with SAS v9.4 (SAS Institute).

Results

Patient Characteristics

A flow diagram of the study population selection is shown in e-Figure 1. Data from 2,836 patients with moderate-to severe OSA (median AHI, 36.0 events/h; interquartile range, 27.0-51.0) were analyzed. The study population consisted of typical patients with OSA with a median age of 58.0 years (interquartile range, 48.0-66.0) who were predominantly male (69%) and with obesity or overweight (median BMI, 30.9 kg/m^2; interquartile

TABLE 1] Description of the Population According to Positive Airway Pressure Therapy Adherence

Characteristic	All	Nonadherent Group	Adherent Group	*P* Value
N	2,836 (100)	982 (34.6)	1,854 (65.4)	…
Age, y	58 (48-66)	56 (46-65)	59 (50-67)	< .0001
Sex, male	1,942 (68.5)	665 (67.7)	1,277 (68.9)	.5273
BMI, kg/m^2	30.9 (27.3-35.2)	30.1 (26.7-35.1)	31.2 (27.5-35.2)	.0004
Living in couple	2,121 (78.8)	687 (74)	1,434 (81.3)	.0001
Educational degree				
No or lower degree	737 (27.8)	243 (26.5)	494 (28.5)	.0016
Technical degree	1,272 (48)	415 (45.2)	857 (49.5)	…
Bachelor or graduate student	642 (24.2)	260 (28.3)	382 (22)	…
Professional situation				
Active	1,248 (46.5)	437 (46.9)	811 (46.2)	< .0001
Inactive	362 (13.5)	182 (19.5)	180 (10.3)	…
Retired	1,076 (40.1)	312 (33.5)	764 (43.5)	…
Medical history				
Atrial fibrillation	368 (13)	117 (11.9)	251 (13.5)	.2208
Heart failure	204 (7.2)	72 (7.3)	132 (7.1)	.8351
Hypertension	1,674 (59)	551 (56.1)	1,123 (60.6)	.0215
Myocardial infarction	246 (8.7)	77 (7.8)	169 (9.1)	.2513
Diabetes	744 (26.2)	258 (26.3)	486 (26.2)	.9727
COPD	389 (13.7)	139 (14.2)	250 (13.5)	.6215
Depression	413 (14.6)	174 (17.7)	239 (12.9)	.0005
Polysomnography	1,092 (38.5)	422 (43)	670 (36.1)	.0004
OSA severity				
Epworth score	10 (7-14)	10 (7-14)	10 (7-14)	.9996
AHI, events/h	36 (27-51)	32 (24-47)	37 (30-53)	<.0001
ODI, events/h	30 (18-46)	26 (16-42)	32 (19-49)	<.0001
T90, %	6 (1-21)	5 (1-18)	7 (1-22)	.0002

Values are expressed as median (25th percentile-75th percentile), No. (%), or as otherwise indicated. Missing values: BMI: n = 5; living in couple: n = 144; educational degree: n = 185; professional situation: n = 150; ODI: n = 22, and T90: n = 16. AHI = apnea-hypopnea index; ODI = 3% oxygen desaturation index; T90 = percentage of sleep (or recording) time with oxygen saturation < 90%.

range, 27.3-35.2), with frequent CV and metabolic comorbidities (Table 1). Significant differences were observed between the nonadherent and adherent groups for age, BMI, socioprofessional status, medical history of hypertension and depression, diagnostic sleep study type, and OSA severity indices.

Adherence to PAP

Median PAP adherence was 5.4 h/d (interquartile range, 1.8-7.1) at 2 years, with 65% of patients considered as PAP adherent (median PAP use, 6.6 h/d; interquartile range, 5.3-7.6). From 982 patients who were nonadherent, 441 used PAP $<$ 4 h/d (median use, 2.85 h/d; interquartile range, 1.91-3.48) and 541 had terminated PAP treatment during the 2 first years of follow-up.

Proxies of Healthy Behaviors

During the 2 years preceding PAP initiation, 62% of patients received at least one CV drug and 43% of them were adherent with an MPR $\geq$ 80% for all CV active drugs. Among female participants aged 50 to 74 years, 74% had a mammogram. Of male participants, 65% had a PSA test, and 42% of the target population received an influenza vaccination. Previous history of drowsiness-related near-missed or car accidents was reported in 17% of patients in the 2 years preceding PAP initiation.

Association of Healthy Behaviors With Subsequent PAP Adherence

Patients who were PAP adherent more frequently had never smoked ($P < .0001$), were adherent to CV drugs ($P < .0001$), performed more PSA testing ($P < .0001$), and reported less drowsiness-related near-missed or car accidents ($P = .0052$) during the 2 years preceding PAP initiation (Table 2). Figure 2 illustrates the dose-response relationship between adherence to CV active drugs (MPR) and subsequent PAP adherence. The relationship appeared stronger for antihypertensive and lipid-lowering medications than for beta blockers and antiplatelet agents.

No association was found between breast cancer screening, influenza vaccination, and future PAP adherence.

The findings of multivariable mixed logistic regression analyses evaluating the independent association of proxies with subsequent PAP adherence vs nonadherence and PAP termination are presented in Figure 3 and e-Table 2. The results show that future adherence to PAP in comparison with nonadherence to PAP was significantly associated with adherence to all CV drugs (OR, 1.43; 95% CI, 1.15-1.77), adherence to lipid-lowering drugs (OR, 1.35; 95% CI, 1.04-1.76), adherence to antihypertensive drugs (OR, 1.67; 95% CI, 1.29-2.16), and no tobacco consumption (OR, 1.37; 95% CI, 1.10-1.71).

Adherence to all CV drugs (OR, 1.59; 95% CI, 1.22-2.07), adherence to lipid-lowering drugs (OR, 1.46; 95% CI, 1.07-1.99), adherence to antihypertensive drugs (OR, 1.89; 95% CI, 1.40-2.55), sleepiness-related near-missed or car accidents (OR, 1.39; 95% CI, 1.04-1.87), and no tobacco consumption (OR, 1.35; 95% CI, 1.03-1.78) were also significantly associated with a higher likelihood of PAP continuation with good adherence in comparison with PAP termination.

Health Care Resource Use

Figure 4 presents health care resource use according to PAP therapy adherence 2 years before and 2 years after PAP initiation and shows that patients who were PAP adherent use less health care resources both before and after PAP initiation than patients who were nonadherent.

Discussion

To our knowledge, this is the first study evaluating the association between surrogate markers of the HAE and subsequent adherence to PAP therapy for OSA. The study demonstrates that proxies of the HAE (eg, adherence to CV active drugs, no history of smoking, sleepiness-related car accidents) were associated with subsequent PAP adherence and continuation after adjustment for confounders. Our findings regarding health care resources use suggest that patients who are adherent were healthier prior to PAP prescription.

Few studies have examined the association between drug adherence as proxy of the HAE and PAP therapy adherence. In a cohort of 2,158 patients with severe OSA concomitantly treated with PAP and CV active drugs, the average 2-year MPR for antihypertensives, statins, and antiplatelets was not different between patients who were PAP adherent and patients who were nonadherent.[19] Conversely, in a retrospective cohort study, Platt et al[18] found that patients with low adherence to lipid-lowering drugs prior to PAP initiation were less likely to be subsequently adherent to PAP therapy over the first week of use. Interestingly, married patients were more adherent to both medications and PAP, and inclusion of marital status in the multivariable analysis reduced to no significance in

TABLE 2] Proxies of Healthy Behaviors According to Positive Airway Pressure Therapy Adherence

Variable	All	Nonadherent Group	Adherent Group	*P* Value
Alcohol consumption	1,231 (44.5)	399 (41.7)	832 (46)	.0314
Tobacco consumption				
Active tobacco use	569 (20.1)	248 (25.3)	321 (17.3)	< .0001
Previously used tobacco	1,088 (38.4)	347 (35.3)	741 (40)	…
Never used tobacco	1,179 (41.6)	387 (39.4)	792 (42.7)	…
Adherence to CV drugs[a]				
All CV active drugs (n = 1,763)				
MPR	1 (0.794-1)	0.954 (0.688-1)	1 (0.843-1)	< .0001
MPR ≥ 80%	753 (42.7)	214 (36.3)	539 (45.9)	.0001
Antiplatelet agents (n = 752)				
MPR	0.942 (0.621-1)	0.915 (0.555-1)	0.956 (0.657-1)	.0252
MPR ≥ 80%	505 (67.2)	175 (63.4)	330 (69.3)	.0956
Beta blockers (n = 794)				
MPR	0.878 (0.309-1)	0.851 (0.307-1)	0.903 (0.315-1)	.0897
MPR ≥ 80%	443 (55.8)	143 (52.4)	300 (57.6)	.1610
Lipid-lowering drugs (n = 1,186)				
MPR	0.882 (0.569-1)	0.841 (0.436-1)	0.9 (0.635-1)	.0003
MPR ≥ 80%	458 (38.6)	217 (55.6)	511 (64.2)	.0045
Antihypertensive drugs (n = 1,378)				
MPR	0.978 (0.786-1)	0.935 (0.706-1)	1 (0.831-1)	< .0001
MPR ≥ 80%	1,019 (73.9)	301 (66.9)	718 (77.4)	< .0001
Adherence to cancer screening tests[a]				
Mammogram (n = 613)	453 (73.9)	159 (73.6)	294 (74.1)	.9235
PSA test (n = 1,203)	787 (65.4)	274 (41.2)	660 (51.7)	< .0001
Adherence to influenza vaccination[a] (n = 1,724)	721 (41.8)	182 (37.2)	385 (42)	.0827
Drowsiness-related road accident (n = 1,986)	145 (17.3)	159 (18.6)	241 (14.4)	.0052

Values are expressed as median (25th percentile-75th percentile), No. (%), or as otherwise indicated. The proxies of healthy adherer effect were collected from the database during the 2 y preceding positive airway pressure initiation. CV = cardiovascular; MPR = medication possession ratio; PSA = prostate-specific antigen.

[a]For each proxy of healthy behaviors (adherence to CV active drugs, cancer screening tests, influenza vaccination), the multivariable analysis of its association with subsequent positive airway pressure adherence was restricted to the subgroup of patients concerned by the treatment or preventive measure.

the association of drug and PAP adherence. Consistent with this, our study provides evidence that patients who are adherent to chronic CV active medications are more likely to be PAP adherent after adjustment for major confounders including marital status, which has been associated with PAP and medication adherence.[20,27] There were differences between healthy behaviors in terms of their relationship with subsequent PAP adherence, with the association being stronger for antihypertensive and lipid-lowering drugs than for the other measures. Although these differences should be interpreted with caution due to the unbalanced sample size, they suggest that the underlying causes of healthy behaviors may not be fully captured by measuring a single behavior. Contrary to the data previously reported regarding adherence to statins,[13,14] we failed to demonstrate any association of cancer screening tests and influenza vaccination with subsequent PAP adherence. Given the low number of events expected in the target population, this negative result might be due to insufficient statistical power. Healthy lifestyle can also include avoidance of risky behaviors. Dormuth et al[14] demonstrated an association between good adherence to statins and reduced risk of accidental events that are not

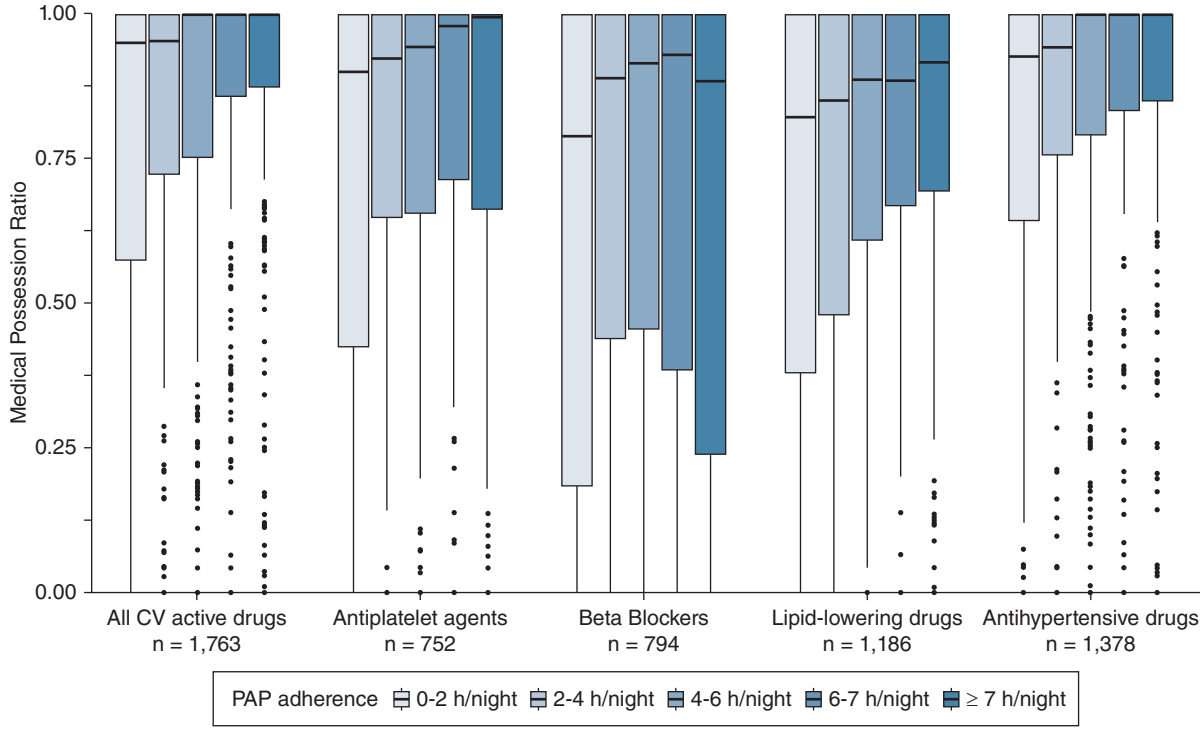

Figure 2 – *Relationship between adherence to CV active drugs (medication possession ratio) and subsequent PAP adherence. CV = cardiovascular; PAP = positive airway pressure.*

known to be causally affected by statin exposure (eg, workplace and motor vehicle accidents). Similarly, we found that patients with no history of sleepiness-related near-missed or car accidents had a lower risk of PAP termination after adjustment for confounders including OSA severity. A previous study from our group has demonstrated an association between risk attitude in the health/safety domain and the risk of PAP termination in patients with newly diagnosed OSA.[28] Patients with risk-seeking behaviors in daily life according to the Domain Specific Risk-Taking Scale were more likely to discontinue PAP.

Although RCTs are considered the criterion standard for assessing treatment effectiveness, they are not without limitations (eg, low external validity), which is particularly relevant in the field of OSA.[7] Consequently, real-world data have gained an increased interest because they might be able to provide a more generalizable picture of the effects of routine clinical use of PAP on health outcomes. However, many covariates, some of which are not routinely captured in health care data sets, including socioenvironmental factors, diet, exercise, and sleep duration, are relevant to the assessment of CV outcomes in the context of PAP adherence.[12] Our results contribute to a growing collection of evidence in support of healthy adherer associations between PAP therapy and numerous other health outcomes. Our findings suggest that the HAE might be partly detectable by examining the association of PAP adherence with the adherence to CV active drugs, smoking habits, and occurrence of sleep-related car accidents. Adherence to chronic CV active medications was entered as a covariate in a recent study from our group evaluating the dose-response relationship between PAP adherence and incident major adverse CV events. The association remained significant after adjusting demographics, socioeconomic status, comorbidities, alcohol intake, tobacco consumption, and concomitant CV drugs MPR.[25] Further real-life cohort studies enriched with additional covariates (eg, diet, physical activity, sleep diary) should help to better elucidate the complex relationship between PAP adherence and CV risk, and to develop methods to adjust for it in observational studies. However, residual confounding by the HAE is difficult to address. Even after accounting for demographics, socioeconomic status, comorbidities, and healthy behaviors (eg, physical activity, diet), previous RCTs have estimated that the risk of mortality is 50% greater in those who are nonadherent to placebo medications compared with those who are adherent.[29-31] Controlling for past

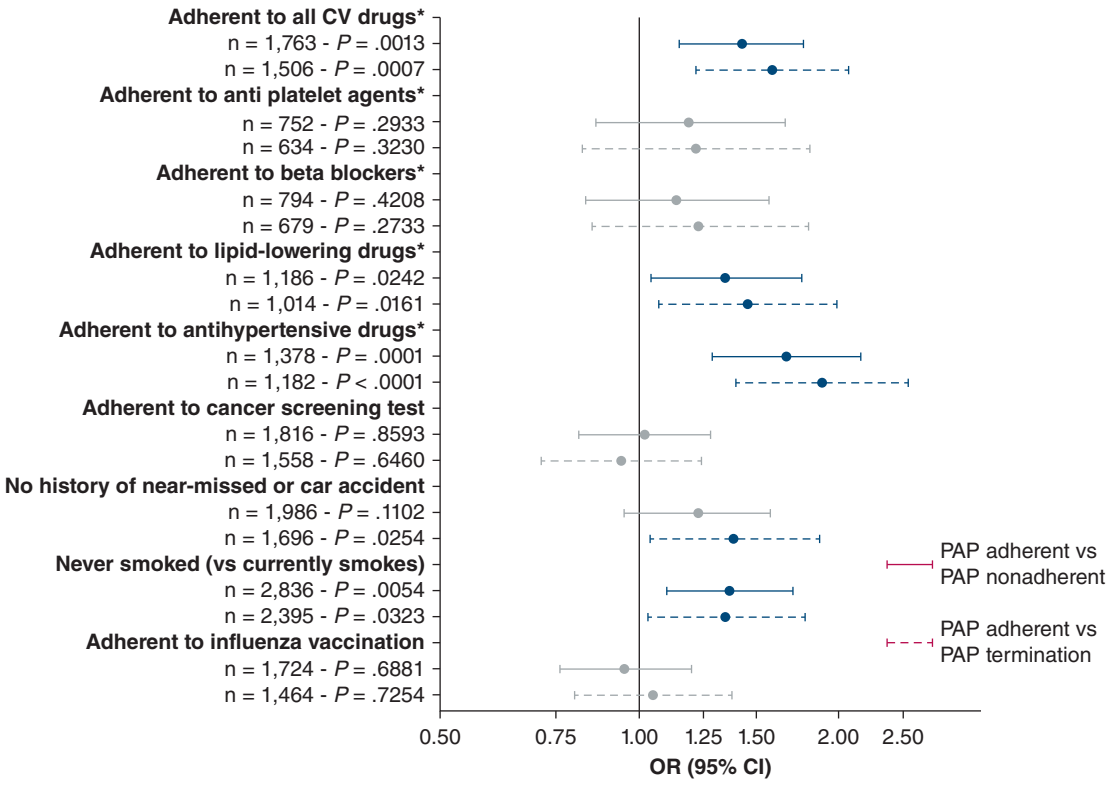

Figure 3 – *Forest plot illustrating the logistic regression analysis of proxies of healthy behaviors associated with subsequent PAP adherence. Multivariable mixed logistic regression models were adjusted for age, sex, BMI, tobacco consumption, socioeconomic factors (marital status and educational level), apnea-hypopnea index, diabetes, depression, hypertension, history of cardiovascular diseases, and number of general practitioner consultations. CV = cardiovascular; PAP = positive airway pressure. *Patients with medical possession ratio ≥ 80% were considered as treatment adherent.*

adherence to treatments and novel study designs (eg, new user design using active comparator) are promising methods.[13,32]

Recent studies have reported an inverse dose-response relationship between daily PAP use and health care consumption derived from administrative medical/pharmacy claims data in the United States.[33,34] Being based solely on administrative data, several factors (eg, OSA severity, BMI, smoking and alcohol consumption, socioeconomic status) were not available and adjusted for in these studies. The association of PAP adherence with 3-year health care costs has been also identified among participants from the Tele-OSA clinical trial.[3] Another interesting finding of our study is that the lower health care consumption among patients who were PAP adherent vs nonadherent was already present and even more marked before PAP initiation, suggesting that patients who were adherent were healthier prior to OSA diagnosis and device initiation. The negative impact of comorbidities (eg, diabetes, COPD) on PAP continuation has been previously demonstrated.[35] Patients with a high care burden might not prioritize PAP therapy, particularly when OSA is minimally symptomatic. Comorbidities with impact on functional or cognitive capacity may also hinder PAP use. Our results suggest that the association of PAP adherence with health care consumption should not be interpreted without adjusting for past health care resource use.

The strengths of this study include a multicenter design, long and complete follow-up with access to SNDS data and objective measurement of PAP adherence, and a large sample of unselected patients, suggesting generalizability to most PAP-treated patients with OSA. Some limitations should however be noted. Because health care services are mostly free in France, these results could differ in countries with different health systems that involve social and economic barriers to medication adherence. Although MPR is the most commonly used method for calculating adherence to single medications from pharmacy dispensing records,[36] it does not directly assess actual daily pill taking, and assessment of drug adherence was restricted to those who accepted treatment initiation. This might therefore result in

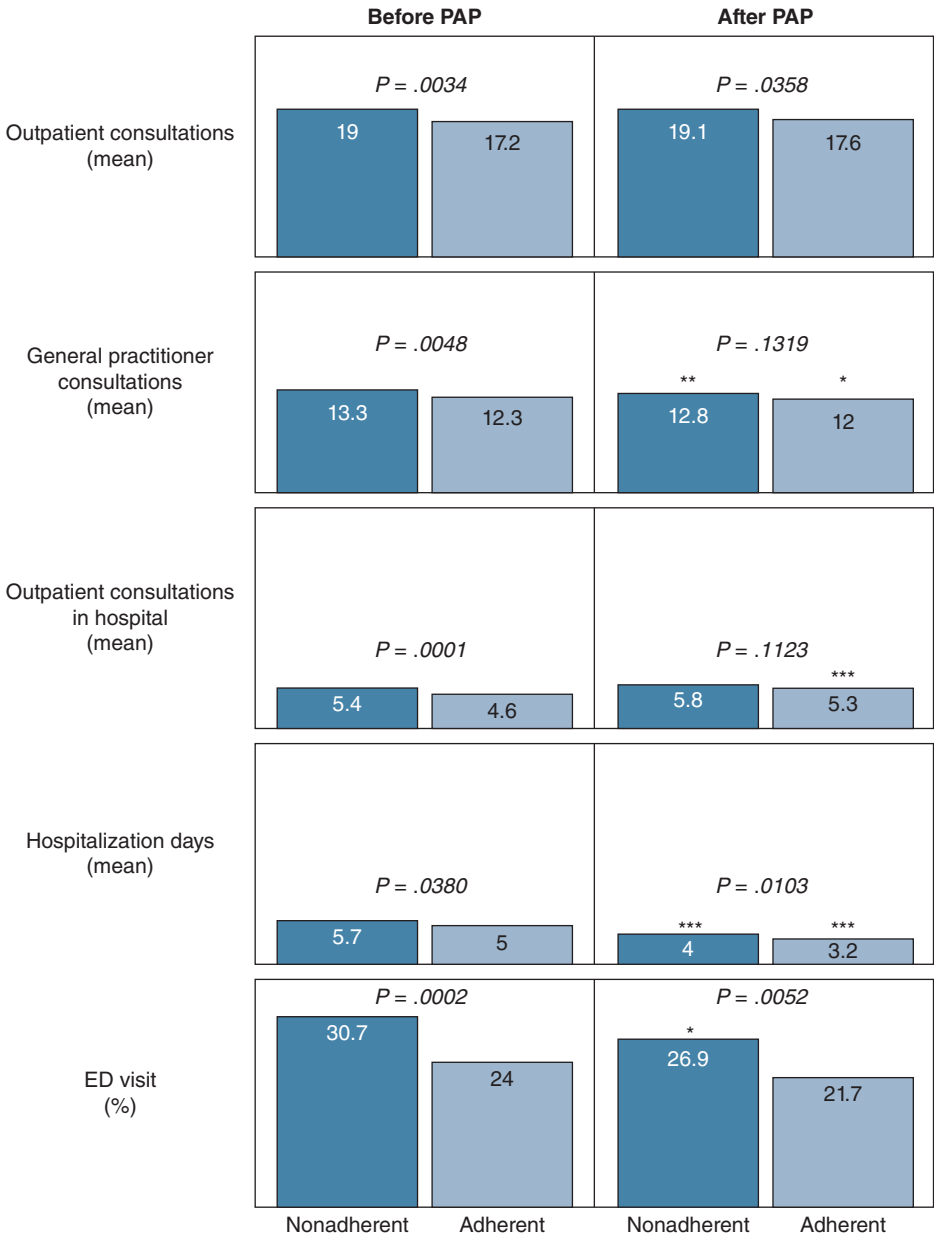

Figure 4 – *Health care resource use according to PAP therapy adherence 2 y before and 2 y after PAP initiation.* P *value presented in the box corresponds to the comparison between patients who were adherent and nonadherent using nonparametric Mann-Whitney U test. PAP = positive airway pressure.* *P < .05; **P < .01; ***P < .0001 *for the comparison of patients after vs before PAP initiation using Wilcoxon signed-rank test for paired values and McNemar test for ED visit comparisons.*

some degree of drug adherence misclassification. Similarly, the assessment of other healthy behaviors (eg, cancer screening tests, influenza vaccinations) may also lack standardized criteria to some extent, which could introduce measurement bias. The pregnancy criteria for influenza vaccination in women and the choice to prescribe or not PSA tests at the individual level in men aged 50 to 74 years were not available in the database.

We also acknowledge that unmeasured factors (eg, nutrition, physical activity, social support, psychological factors) are other healthy behaviors potentially explaining the HAE. Future studies are needed to explore in more depth the underlying factors linking healthy behaviors with PAP adherence. Moreover, reasons for outpatient consultations, hospitalizations, and ED visits were not known, which may limit the interpretation of our findings.

Interpretation

Patients who adhere to PAP therapy for OSA are more health-seeking and use less health care resources prior to device initiation than patients who are nonadherent. Until the HAE associated with PAP adherence is better understood, caution is warranted when interpreting the association of PAP adherence with CV health outcomes and health care resource use.

Funding/Support

This study was supported by the Pays de la Loire Research Institute.

Financial/Nonfinancial Disclosures

The authors have reported to *CHEST* the following: C. L. reports lecture honoraria from Resmed. W. T. reports lecture honoraria from Astra Zeneca and travel support from Asten. F. Gagnadoux reports grants from Resmed; consulting fees from Resmed, Sefam, Inspire, and bioprojet; lecture honoraria from Philips Respironics, Inspire, Resmed, Bioprojet, and Asten Sante; and travel support from Asten Sante, MSD, and Bioprojet. None declared (S. B., A. S., T. P., C. H., P. M., A. B.-T., N. M., S. K., F. Goupil).

Acknowledgments

Author contributions: F. Gagnadoux obtained funding for the study. C. L., S. B., and F. Gagnadoux designed the study. F. Goupil, T. P., C. H., P. M., A. B.-T., N. M., W. T., S. K., and F. Gagnadoux were involved in the data collection. S. B. had full access to all data in the study and analyzed the data. C. L., S. B., and F. Gagnadoux interpreted data. C. L. drafted the manuscript. S. B., A. S., and F. Gagnadoux critically revised the manuscript. All authors read and approved the final manuscript as submitted. C.L., S.B., and F. Gagnadoux are responsible for the content of the manuscript.

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Role of the sponsors: The funders had no role in the design of the study; in the collection, analysis, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Other contributions: We thank the Pays de la Loire Research Institute, promoter of the IRSR des Pays de la Loire Sleep Cohort, and the National Health Insurance Fund for giving us access to the French administrative health care database.

Additional information: The e-Figure and e-Tables are available online under "Supplementary Data."

References

1. Benjafield AV, Ayas NT, Eastwood PR, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med*. 2019;7(8):687-698.
2. Lévy P, Kohler M, McNicholas WT, et al. Obstructive sleep apnoea syndrome. *Nat Rev Dis Primer*. 2015;1:15015.
3. An J, Glick HA, Sawyer AM, et al. Association between positive airway pressure adherence and health care costs among individuals with OSA. *Chest*. 2023;163(6):1543-1554.
4. McEvoy RD, Antic NA, Heeley E, et al. CPAP for prevention of cardiovascular events in obstructive sleep apnea. *N Engl J Med*. 2016;375(10):919-931.
5. Peker Y, Glantz H, Eulenburg C, Wegscheider K, Herlitz J, Thunström E. Effect of positive airway pressure on cardiovascular outcomes in coronary artery disease patients with nonsleepy obstructive sleep apnea. The RICCADSA randomized controlled trial. *Am J Respir Crit Care Med*. 2016;194(5):613-620.
6. Sánchez-de-la-Torre M, Sánchez-de-la-Torre A, Bertran S, et al. Effect of obstructive sleep apnoea and its treatment with continuous positive airway pressure on the prevalence of cardiovascular events in patients with acute coronary syndrome (ISAACC study): a randomised controlled trial. *Lancet Respir Med*. 2020;8(4):359-367.
7. Reynor A, McArdle N, Shenoy B, et al. Continuous positive airway pressure and adverse cardiovascular events in obstructive sleep apnea: Are participants of randomized trials representative of sleep clinic patients? *Sleep*. 2022;45(4):zsab264.
8. Marin JM, Carrizo SJ, Vicente E, Agusti AGN. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet*. 2005;365(9464):1046-1053.
9. Buchner NJ, Sanner BM, Borgel J, Rump LC. Continuous positive airway pressure treatment of mild to moderate obstructive sleep apnea reduces cardiovascular risk. *Am J Respir Crit Care Med*. 2007;176(12):1274-1280.
10. Pépin J-L, Bailly S, Rinder P, et al. Relationship between CPAP termination and all-cause mortality: a French nationwide database analysis. *Chest*. 2022;161(6):1657-1665.
11. Pépin J-L, Tamisier R, Benjafield AV, et al. CPAP resumption after a first termination and impact on all-cause mortality in France. *Eur Respir J*. 2024;63(2):2301171.
12. Bailly S, Trzepizur W, Gagnadoux F. Cardiovascular protection in sleep apnea: Is it a question of CPAP adherence? *Arch Bronconeumol*. 2023;59(5):277-279.
13. Brookhart MA, Patrick AR, Dormuth C, et al. Adherence to lipid-lowering therapy and the use of preventive health services: an investigation of the healthy user effect. *Am J Epidemiol*. 2007;166(3):348-354.
14. Dormuth CR, Patrick AR, Shrank WH, et al. Statin adherence and risk of accidents: a cautionary tale. *Circulation*. 2009;119(15):2051-2057.
15. Simpson SH, Eurich DT, Majumdar SR, et al. A meta-analysis of the association between adherence to drug therapy and mortality. *BMJ*. 2006;333(7557):15.
16. Kapur VK, Psaty BM. Obtaining valid estimates of the effect of CPAP therapy: reducing healthy adherer and other biases in observational studies. *Chest*. 2022;161(6):1444-1445.
17. Kunisaki KM. CPAP adherence and cardiovascular disease: beware of the healthy adherer effect. *Sleep Breath*. 2020;24(2):599-600.
18. Platt AB, Kuna ST, Field SH, et al. Adherence to sleep apnea therapy and use of lipid-lowering drugs: a study of the healthy-user effect. *Chest*. 2010;137(1):102-108.
19. Villar I, Izuel M, Carrizo S, Vicente E, Marin JM. Medication adherence and persistence in severe obstructive sleep apnea. *Sleep*. 2009;32(5):623-628.
20. Gagnadoux F, Le Vaillant M, Goupil F, et al. Influence of marital status and employment status on long-term adherence with continuous positive airway pressure in sleep apnea patients. *PloS One*. 2011;6(8):e22503.
21. Justeau G, Gervès-Pinquié C, Le Vaillant M, et al. Association between nocturnal hypoxemia and cancer incidence in patients investigated for OSA: data from a large multicenter French cohort. *Chest*. 2020;158(6):2610-2620.

22. Meurice J-C, Gagnadoux F. Recommendations for clinical practice in the management of obstructive sleep apnea syndrome in adults. Preface. *Rev Mal Respir*. 2010;27(suppl 3):S113-S114.

23. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med*. 2012;8(5):597-619.

24. Canfield SL, Zuckerman A, Anguiano RH, et al. Navigating the wild west of medication adherence reporting in specialty pharmacy. *J Manag Care Spec Pharm*. 2019;25(10):1073-1077.

25. Gervès-Pinquié C, Bailly S, Goupil F, et al. Positive airway pressure adherence, mortality, and cardiovascular events in patients with sleep apnea. *Am J Respir Crit Care Med*. 2022;206(11):1393-1404.

26. van Buuren S, Groothuis-Oudshoorn K. mice: multivariate imputation by chained equations in R. *J Stat Softw*. 2011;45(3):1-67.

27. Freak-Poli R, Hu J, Phyo AZZ, Barker F. Does social isolation, social support or loneliness influence health or well-being after a cardiovascular disease event? A narrative thematic systematic review. *Health Soc Care Community*. 2022;30(1):e16-e38.

28. Pelletier-Fleury N, Le Vaillant M, Goupil F, et al. Risk-seeking attitude in health and safety domain is associated with continuous positive airway pressure discontinuation in patients with obstructive sleep apnea-a multicenter prospective cohort study. *Sleep*. 2021;44(2):zsaa156.

29. Donovan LM, Patel SR. The challenges of estimating causal effects of continuous positive airway pressure therapy from observational data. *Am J Respir Crit Care Med*. 2022;206(12):1570-1571.

30. Curtis JR, Larson JC, Delzell E, et al. Placebo adherence, clinical outcomes, and mortality in the women's health initiative randomized hormone therapy trials. *Med Care*. 2011;49(5):427-435.

31. Pinsky P, Goodman P, Parnes H, Ford L, Minasian L. Adherence with protocol medication use and mortality from unrelated causes in a prevention trial. *Prev Med*. 2021;153:106778.

32. Solomon DH, Avorn J, Stürmer T, Glynn RJ, Mogun H, Schneeweiss S. Cardiovascular outcomes in new users of coxibs and nonsteroidal antiinflammatory drugs: high-risk subgroups and time course of risk. *Arthritis Rheum*. 2006;54(5):1378-1389.

33. Malhotra A, Sterling KL, Cistulli PA, et al. Dose-response relationship between obstructive sleep apnea therapy adherence and healthcare utilization. *Ann Am Thorac Soc*. 2023;20(6):891-897.

34. Sterling KL, Alpert N, Cistulli PA, et al. Healthcare resource utilisation and costs in patients with treated obstructive sleep apnea. *J Sleep Res*. 2023e14099.

35. Pépin J-L, Bailly S, Rinder P, et al. CPAP therapy termination rates by OSA phenotype: a French nationwide database analysis. *J Clin Med*. 2021;10(5):936.

36. Andrade SE, Kahler KH, Frech F, Chan KA. Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiol Drug Saf*. 2006;15(8):565-574.