Positive airway pressure treatment affects respiratory symptoms and gastro-oesophageal reflux: the Icelandic Sleep Apnea Cohort Study

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Shareable abstract (@ERSpublications)
Treating OSA patients with PAP decreases nocturnal gastro-oesophageal reflux (nGOR), wheezing and productive cough. PAP treatment directly affects nGOR and wheezing, while the effect on productive cough is mostly mediated through a decrease in nGOR. https://bit.ly/3QotRCW

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Abstract

Aim To study the effect of positive airway pressure (PAP) treatment on nocturnal gastro-oesophageal reflux (nGOR) and respiratory symptoms among clinical obstructive sleep apnoea (OSA) patients.

Methods 822 patients newly diagnosed with OSA referred for PAP treatment were recruited. 732 patients had a 2-year follow-up visit with continuous PAP compliance data (366 full PAP users, 366 partial/non-PAP users). They answered questionnaires, including reporting of nGOR, sleep and respiratory symptoms and general health. Patients with nGOR symptoms once a week or more were defined as "with nGOR". Those without nGOR symptoms and nGOR medication were defined as "no nGOR". Others were defined as "possible nGOR".

Results At 2-year follow-up, PAP treatment among full users resulted in decreased nGOR (adjusted OR 0.58, 95% CI 0.40–0.86) and wheezing (adjusted OR 0.56, 95% CI 0.35–0.88) compared with partial/non-PAP users. Decreased nGOR, among both full and partial/non-users of PAP treatment, was associated with a decrease in productive morning cough (adjusted OR 4.70, 95% CI 2.22–9.99) and a decrease in chronic bronchitis (adjusted OR 3.86, 95% CI 1.74–8.58), but not decreased wheezing (adjusted OR 0.90, 95% CI 0.39–2.08). A mediation analysis found that PAP treatment directly led to a decrease in wheezing, not mediated through nGOR. Conversely, PAP treatment decreased productive cough mediated through a decrease in nGOR.

Conclusion In an unselected group of OSA patients, PAP treatment for 2 years was associated with a decrease in nGOR and respiratory symptoms. The PAP treatment itself was associated with less wheezing. A decrease in nGOR through PAP treatment was associated with a decrease in productive cough.

Introduction

Respiratory symptoms are more common among obstructive sleep apnoea (OSA) patients than in comparable general population samples [1]. Patients with OSA also have a much higher prevalence of nocturnal gastro-oesophageal reflux (nGOR) [2, 3]. This higher prevalence of nGOR is likely caused by additional strain on the gastro-oesophageal junction from the increased respiratory effort in OSA [4]. The increase in respiratory symptoms in OSA may at least in part be mediated through nGOR [1], because nGOR may cause airway irritation through microaspirations [5].

Positive airway pressure (PAP) treatment is one of the most effective and most used treatments for OSA, especially more severe or symptomatic OSA [6]. Severity is usually graded by the apnoea–hypopnoea index (AHI) but, importantly, patients with OSA with a similar AHI may differ significantly in symptoms and comorbidities [7, 8]. Therefore, symptom burden is a key factor to also consider when deciding on OSA treatment [6]; ideally, all symptoms attributable to OSA should be included.

Recent studies have reported that OSA treatment with PAP decreases wheezing and improves asthma control [9–11]. PAP treatment may also diminish nGOR through increased tonus in the lower oesophageal sphincter and fewer swings in intrathoracic pressure with PAP treatment [12]. In clinical studies on OSA patients, PAP treatment seems to diminish nGOR, as shown in a recent meta-analysis, although a general lack of control groups hinders strong conclusions [13–15].

It is still unclear how PAP treatment in OSA affects the complex associations between OSA and respiratory symptoms in general, and the role of nGOR in particular. Given the high prevalence of OSA, nGOR and respiratory symptoms, more knowledge on their possible causative associations and response to treatment is of significant clinical and public health importance. This knowledge could ultimately lead to more efficient and personalised treatment, possibly changing treatment decisions for a considerable number of OSA patients who often are not offered PAP treatment today, particularly those with a low AHI but respiratory symptoms and nGOR.

The aim of this study was to examine changes in respiratory symptoms and nGOR in a large group of well-defined clinical OSA patients, before and 2 years after starting PAP treatment. PAP use was assessed and related to changes in respiratory symptoms. Mediation analyses were then performed to understand whether changes in respiratory symptoms with PAP treatment were mediated through a concomitant effect of PAP on nGOR.

Material and methods

Study sample and design

This study used data from the Icelandic Sleep Apnea Cohort (ISAC) study, described previously in detail [16–19]. The population consisted of 822 patients diagnosed with moderate to severe OSA (AHI $\geqslant$15 events·h^{-1}) in the entire population of Iceland, who initiated treatment with PAP from September 2005 to December 2009. At baseline, before starting PAP treatment, participants completed a type 3 sleep study and answered detailed questionnaires including the Basic Nordic Sleep Questionnaire (BNSQ), as previously described [16, 18, 19]. A follow-up visit 2 years after treatment initiation examined treatment adherence to PAP (see below) and repeated baseline assessments [16]. This follow-up was completed in 738 patients (90.1%), 732 (99.2%) of whom responded to questions regarding nGOR at follow-up.

Participants were defined as non-users, partial PAP users or full PAP users according to the amount and frequency of PAP use (see “PAP use”, below). Prevalence of nGOR was analysed by symptom responses on the BNSQ and by medication use (see “Nocturnal gastro-oesophageal reflux”, below).

The ISAC study was approved by the National Bioethics Committee and the Data Protection Authority of Iceland and by the Institutional Review Board of the University of Pennsylvania. Written consent was obtained from all research participants.

Nocturnal gastro-oesophageal reflux

The definition of nGOR was based on symptoms reported on the BNSQ and nGOR medication use, in the same manner at baseline and follow-up. nGOR symptoms were defined using the following question regarding symptoms in the previous 4 weeks: “Do you have heartburn or belching when you have gone to bed?” [20, 21]. Answers were rated on a five-point scale: never/almost never (1 point), less than once a week (2 points), once or twice a week (3 points), three to five times a week (4 points) or every day or almost every day of the week (5 points). Participants with symptoms once a week or more were defined as “with nGOR”. Those who almost never had nGOR symptoms and were not using medication for nGOR were defined as “without nGOR”. Others were defined as “possible nGOR”.

Respiratory symptoms

The questions used for analysing respiratory symptoms were the same as in the Burden of Obstructive Lung Diseases (BOLD) initiative [22]. In short, questions asked whether participants experienced symptoms such as wheezing or productive cough in the previous year. Participants reporting

productive cough most days for at least 3 months per year for at least the last 2 years were said to have chronic bronchitis.

Covariates

Participants answered standardised questionnaires about their health and sleep including questions about smoking and whether they had hypertension and/or diabetes (medical diagnosis and medication), or cardiovascular diseases such as a medical diagnosis of coronary artery occlusion (ischaemic heart disease), heart failure and stroke. Excessive daytime sleepiness was defined as reporting feeling sleepy or drowsy during the day, 3 days·week^{-1} or more.

Sleep recording in ISAC cohort

Prior to PAP treatment, all patients with OSA had a sleep study with an Embletta type 3 portable monitor or an Embla 12 channel system (Natus Medical Inc., Ontario, Canada) or a T3 device (Nox Medical, Reykjavik, Iceland), as previously described [16, 19]. No difference was seen in sleep variables between participants with and without nGOR at baseline.

PAP use

All patients prescribed PAP received care at the Department of Respiratory Medicine and Sleep, Landspitali University Hospital. Patients on PAP had direct access to the outpatient clinic where trained staff helped them to find the type of PAP device and settings they needed.

PAP adherence at the 2-year follow-up was obtained from downloads of usage in the previous 4 weeks from memory cards (available for 77.6% of PAP users) from ResMed S8 machines (ResMed Corp., San Diego, CA, USA). Other participants had older PAP devices that did not allow for this type of evaluation, in which case self-reported adherence data were used. Self-reported data on usage were collected from all patients at the follow-up, and had 98.6% sensitivity and 45.1% specificity in distinguishing full users from partial users when compared to objective data. For further details, see our previous publications [16, 19].

"Full PAP users" (n=366) were defined as those patients who used PAP for ⩾20 days and ⩾4 h·day^{-1} on average for the previous 4 weeks based on objective data, or ⩾5 nights·week^{-1} for ⩾60% of the night based on questionnaire responses. PAP users not meeting criteria for full users were classified as "partial PAP users" (n=103). Those who had returned their PAP device within 1 year of therapy initiation were defined as "non-users" (n=263). For dichotomous comparisons, "partial PAP users" and "non-users" were combined as "non/partial PAP users" (n=366) and compared with "full PAP users".

No significant difference in PAP usage hours the past 28 nights was seen between nGOR groups defined at baseline, where average use per night (mean±SD) was as follows: no nGOR 6.0±2.0 h; possible nGOR 6.2±2.1 h (p=0.36); with nGOR 6.4±2.3 h (p=0.24).

Statistical analyses

Data analysis and mediation modelling

All statistics were calculated with STATA, version 16 (Stata Corporation, College Station, TX, USA). A p-value <0.05 was considered statistically significant.

First, baseline characteristics of the OSA patients by PAP treatment groups were analysed using descriptive statistics. Second, as an initial part of mediation analysis, we analysed the effect of PAP usage on changes in nGOR and respiratory symptoms. Descriptive statistics and logistic regression models were used to compare changes in nGOR and respiratory symptoms between PAP treatment groups (ordinal logistic regression for nGOR analysis). Then, the same analysis was performed again while weighting the results using a propensity score-based weight (described further below). Third, we used logistic regression to analyse the association between post-treatment nGOR status and post-treatment respiratory symptoms,

FIGURE 1 Theoretical model for the association between positive airway pressure (PAP) treatment, nocturnal gastro-oesophageal reflux (nGOR) and respiratory symptoms, where nGOR is a mediator for the association between PAP treatment and respiratory symptoms.

adjusted for the symptom status at baseline and using the aforementioned propensity score-based weight. Fourth, we performed a mediation analysis to assess both the direct effect of PAP treatment on respiratory symptoms and effects mediated through changes in nGOR (figure 1). Mediation analysis was performed according to the AGReMA statement [23], using the Karlson–Holm–Breen method [24]. The analysis was performed while adjusting for change in body mass index (BMI) between study visits (a potential mediator) and respective respiratory symptom status at baseline, and using a propensity score-based weighting scheme.

Propensity score modelling

To derive causal estimates from the nonrandomised group comparisons, we used propensity score approaches. The propensity score for being a full PAP user was estimated using the following baseline variables: age, gender, BMI, smoking status, hypertension, diabetes, nGOR and AHI. This propensity score was then used to calculate a "covariate balancing propensity score"-based inverse probability of treatment weighting for estimating the average treatment effect.

The quality of the propensity scores was assessed by calculating standardised differences for all variables in the propensity score, which revealed excellent covariate balance (*e.g.* standardised differences <0.1 for all variables; supplementary figure) [25]. All weights were between 0.5 and 6, and therefore no truncation of weights or exclusion of outliers was needed.

To evaluate the robustness of the associations to unmeasured confounding, we calculated the E-value, which indicates how strongly associated with both exposure and outcome (independent of included covariates) an unmeasured confounder would need to be to negate the observed associations [26].

Results

Baseline characteristics

The flow of participants from baseline to inclusion in the follow-up analyses is illustrated in figure 2. Overall, full PAP users were slightly older, more likely to be male and had higher BMI than non/partial PAP users. They also had a tendency for less current smoking. Also, nGOR was less common and wheezing more common at baseline among full PAP users compared to non/partial PAP users (table 1).

2-year follow-up: PAP treatment effect on nGOR and respiratory symptoms (exposure–mediator and exposure–outcome analysis)

Among full PAP users, the overall decrease in nGOR symptoms ($p<0.01$) and wheezing ($p=0.02$) was larger than in non/partial PAP users. There was also a nonsignificant trend towards a greater decrease in productive cough among full PAP users (table 2). This held true after applying propensity score-based weights, and additionally the association between full PAP use and a decrease in productive morning cough became statistically significant (table 3). These results were moderately robust to unmeasured confounding, given that the E-value suggested that an unmeasured, unrecognised confounder would need

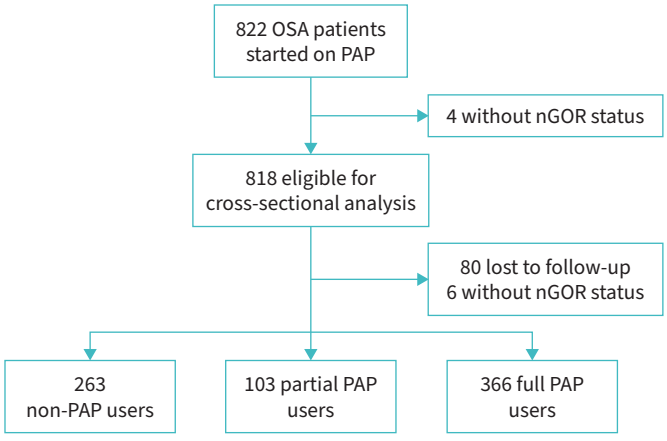

FIGURE 2 Flow chart of the study population. OSA: obstructive sleep apnoea; PAP: positive airway pressure; nGOR: nocturnal gastro-oesophageal reflux.

TABLE 1 Baseline characteristics among participants with follow-up data available

	Non/partial PAP users	Full PAP users	p-value
Patients (n)	366	366	
Age (years), mean±SD	54±10	55±11	0.41
Male	287 (78.4)	301 (82.2)	0.19
BMI (kg·m^{-2}), median (IQR)	31.9 (28.8–35.9)	33.7 (29.9–38.1)	<0.001
Smoking			0.53
Never	103 (28.1)	99 (27.3)	
Former	185 (50.5)	197 (54.3)	
Current	78 (21.3)	67 (18.5)	
Hypertension	140 (38.4)	192 (52.5)	<0.001
ACE inhibitor treatment	34 (9.2)	36 (9.8)	0.80
Diabetes	26 (7.1)	35 (9.6)	0.23
Rhinitis	124 (33.7)	136 (37.0)	0.36
nGOR status			0.11
No nGOR	217 (59.8)	216 (59.2)	
Possible nGOR	87 (24.0)	106 (29.0)	
With nGOR	59 (16.3)	43 (11.8)	
Wheezing	100 (29.0)	121 (34.6)	0.11
Productive morning cough	96 (26.8)	95 (26.5)	0.93
Productive daytime cough	93 (26.1)	88 (24.6)	0.64
Chronic bronchitis	88 (25.1)	88 (25.5)	0.89
AHI (events·h^{-1}), mean±SD	40.1±18.4	49.9±21.2	<0.001
Excessive daytime sleepiness	270 (74.2)	280 (76.5)	0.47

Data are presented as n (%), unless otherwise indicated. PAP: positive airway pressure; BMI: body mass index; IQR: interquartile range; ACE: angiotensin-converting enzyme; nGOR: nocturnal gastro-oesophageal reflux; AHI: apnoea–hypopnoea index.

to be associated with an odds ratio of at least 1.9–2.0 with both the exposure and outcome, independent of included covariates, to fully explain these results.

2-year follow-up: nGOR effect on respiratory symptoms (mediator–outcome analysis)

Among all OSA patients, a decrease in nGOR at follow-up was associated with a decrease in productive cough, but not wheezing, after applying propensity score-based weights (table 4). Associations with productive cough were generally robust to unmeasured confounding, with the E-value suggesting an association with an odds ratio of at least 2.7–3.8 with both the exposure and outcome required to fully explain these results.

2-year follow-up: mediation analysis on PAP treatment, nGOR and respiratory symptoms

Based on the theoretical model presented in figure 1, we performed a mediation analysis to evaluate whether PAP treatment affects respiratory symptoms directly or mediated through a decrease in nGOR.

TABLE 2 Persistence of nGOR and respiratory symptoms after PAP treatment in patients with nGOR or respiratory symptoms at baseline

	Non/partial PAP users	Full PAP users	p-value[#]
With nGOR	21/59 (36)	**6/43 (14)**	**<0.01**
Wheezing	57/94 (61)	**56/116 (48)**	**0.02**
Productive morning cough	62/95 (65)	51/93 (55)	0.11
Productive daytime cough	51/92 (55)	40/81 (49)	0.33
Chronic bronchitis	46/85 (54)	43/77 (56)	0.97

Data are presented as prevalence at follow-up and baseline/prevalence at baseline (%). Numbers in bold signify statistically significant differences. PAP: positive airway pressure; nGOR: nocturnal gastro-oesophageal reflux. [#]: calculated using a regression model, adjusting for baseline status of respective symptom.

TABLE 3 Treatment effect of 2 years with PAP (non/partial PAP users *versus* full PAP users) on nGOR and respiratory symptoms at follow-up

	Full PAP users[#]
nGOR[¶]	**0.58 (0.40–0.86)**
Wheezing[+]	**0.56 (0.35–0.88)**
Productive morning cough[+]	**0.62 (0.39–0.98)**
Productive daytime cough[+]	0.82 (0.51–1.33)
Chronic bronchitis[+]	0.90 (0.55–1.48)

Data are presented as OR (95% CI). Treatment effect adjusted for respective symptom status at baseline, changes in body mass index (BMI) and propensity score-based weights. Propensity score based on baseline values for age, gender, BMI, smoking history, nGOR status, apnoea–hypopnoea index, hypertension and diabetes. Numbers in bold signify statistically significant differences. PAP: positive airway pressure; nGOR: nocturnal gastro-oesophageal reflux. [#]: n=366; [¶]: ordinal logistic regression model; [+]: logistic regression model.

These analyses were adjusted for respective symptom status at baseline and change in BMI between study visits, and weighted using propensity score-based weights.

PAP treatment significantly diminished wheezing at follow-up *via* a direct effect, not mediated through nGOR. Conversely, PAP treatment affected productive cough, especially chronic bronchitis, mediated through changes in nGOR (table 5).

Discussion

In this paper, we report that 2 years of PAP treatment leads to less nGOR, wheezing and productive cough among clinical OSA patients, compared with in poorly or non-treated OSA patients. The effect of PAP treatment on wheezing was directly related to the PAP treatment itself, independent of changes in nGOR. The effect of PAP treatment on productive cough was mainly mediated through diminished nGOR.

PAP treatment effect on nGOR and respiratory symptoms

Overall, nGOR diminished among those with good compliance to PAP treatment. PAP treatment has previously been shown to improve nGOR among fully treated patients with OSA [14]. This is likely explained by the fact that PAP treatment leads to increased baseline pressure in the lower oesophageal sphincter, thereby decreasing the risk for nGOR [27]. Our results strengthen the clinical significance of this association by showing the clear improvement in nGOR among OSA patients who were fully adherent to PAP compared to a large group of non-treated/poorly treated OSA patients.

Wheezing also improved with PAP treatment, and productive morning cough improved to a lesser degree. A number of studies have shown that PAP treatment can improve asthma control [11], and our data further strengthen the possible causal association between PAP treatment and improvements in respiratory symptoms such as wheezing.

TABLE 4 Association between nGOR and respiratory symptoms at follow-up (non/partial PAP users and full PAP users combined)

	Possible nGOR at follow-up[#]	With nGOR at follow-up[¶]
Wheezing	0.94 (0.56–1.57)	0.90 (0.39–2.08)
Productive morning cough	0.84 (0.48–1.46)	**4.71 (2.22–9.99)**
Productive daytime cough	1.47 (0.84–2.59)	**2.82 (1.29–6.16)**
Chronic bronchitis	1.39 (0.79–2.42)	**3.86 (1.74–8.58)**

Odds (95% CI) of respiratory symptoms at follow-up by nGOR status at follow-up, adjusted for respective respiratory symptom at baseline, changes in body mass index (BMI) and propensity score-based weights for treatment group. Propensity score based on baseline values for age, gender, BMI, smoking history, nGOR status, apnoea–hypopnoea index, hypertension and diabetes. No nGOR at follow-up was used as the control group. Numbers in bold signify statistically significant differences. nGOR: nocturnal gastro-oesophageal reflux. [#]: n=182; [¶]: n=47.

TABLE 5 Mediation analysis

	Total effect	Direct PAP effect	Mediated by nGOR
Wheezing	**0.57 (0.36–0.91)**	**0.57 (0.36–0.90)**	1.01 (0.97–1.06)
Productive morning cough	0.66 (0.41–1.04)	0.70 (0.44–1.12)	0.93 (0.87–1.00)
Productive daytime cough	0.86 (0.52–1.40)	0.90 (0.55–1.49)	0.95 (0.89–1.01)
Chronic bronchitis	0.92 (0.56–1.53)	0.99 (0.60–1.65)	**0.93 (0.87–0.99)**

Respiratory symptoms at follow-up after 2 years PAP treatment (non/partial PAP users *versus* full PAP users), analysed for direct PAP treatment effect and treatment effect mediated through nGOR. Analysis adjusted for respective respiratory symptom at baseline, changes over follow-up in body mass index (BMI) and propensity score-based weights. Propensity score based on baseline values for age, gender, BMI, smoking history, nGOR status, apnoea–hypopnoea index, hypertension and diabetes. Numbers in bold signify statistically significant differences. Data are presented as OR (95% CI). PAP: positive airway pressure; nGOR: nocturnal gastro-oesophageal reflux.

Productive cough also improved with PAP treatment, albeit to a lesser extent. Productive cough has not been specifically studied before in PAP-treated OSA, but chronic cough in general is associated with OSA, where gastro-oesophageal reflux has been postulated as a possible causative mechanism [10, 28, 29]. Our study strengthens this theory, as further discussed below.

PAP and nGOR effects on wheezing

It is intriguing that nGOR is clearly associated with wheezing in epidemiological studies, both in the general population and among OSA patients, but we did not find that changes in nGOR with PAP treatment affected changes in wheezing. Also, trials on nGOR treatment with proton pump inhibitors have not shown a clinically significant effect on respiratory symptoms [30, 31]. Therefore, it seems that nGOR is not, in general, a significant cause of wheezing. However, it is possible that nGOR and wheezing either have a common causative factor or that wheezing may cause nGOR. For example, among individuals with disorders such as asthma and OSA, the high respiratory effort of these disorders is known to strain the lower oesophageal sphincter and thereby lead to nGOR [11, 32, 33]. Also, as supported by our findings, OSA may directly cause wheezing. This may be mediated through systemic inflammation caused by OSA and through harmful effects on the airways from increased respiratory effort associated with breathing events characteristic of OSA [11]. We therefore hypothesise that OSA may cause both wheezing and nGOR, independently and partly through different mechanisms (figure 3).

PAP and nGOR effects on productive cough

In general, we found that a decrease in nGOR was associated with less productive cough at follow-up, irrespective of confounding factors. PAP treatment also led to less productive cough, mainly mediated through changes in nGOR. As mentioned above, small studies have suggested that PAP treatment may diminish cough. Regarding nGOR, a general population study on chronic cough found that nGOR was most prevalent among those with productive cough [34]. Persistent nGOR can lead to new onset of nocturnal cough [35]. Also, patients undergoing surgical intervention for gastro-oesophageal reflux have a significant decrease in cough after surgery [36].

One possible mechanism explaining this association is through a vagal nerve reflex, initiated by gastric contents in the distal oesophagus leading to neural reflexes in the bronchi [5]. This is supported by a study finding increased substance P in exhaled biosamples, a sign of neurogenic inflammation, among individuals with nGOR and nocturnal cough [1]. However, that study did not consider OSA, and did not specifically assess productive cough. Therefore, further studies are needed to better understand this

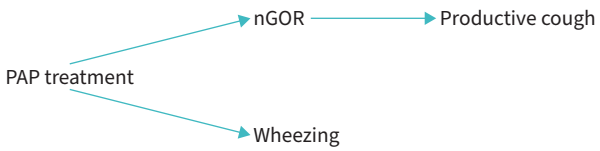

FIGURE 3 Hypothetical model of the association between obstructive sleep apnoea (OSA), nocturnal gastro-oesophageal reflux (nGOR) and respiratory symptoms (wheezing and productive cough).

association. The current results add further evidence that OSA may, in part through increased nGOR, lead to increased productive cough (figure 3).

Clinical implications

This study has some clinical implications. First, OSA patients with nGOR are likely to show improvement in nGOR symptoms with PAP treatment when adequately adherent. Second, different respiratory symptoms among patients with OSA may respond differently to PAP treatment. Wheezing may likely respond to PAP treatment, irrespective of concomitant nGOR, while productive cough responds less well, and possibly only among patients with concomitant nGOR. Collectively, the results also indicate that irrespective of AHI, patients with OSA may benefit from PAP treatment if they have considerable nGOR and respiratory symptoms.

Strengths and weaknesses

The main strengths of this study are the well-characterised, unselected, clinical OSA cohort, with a relatively long follow-up time of 2 years, including patients with and without PAP treatment. Also, statistical methods including propensity score-based weights diminish the inherent problems in comparing somewhat different cohorts, in this case OSA patients who adhere to PAP treatment with those who do not. We also leveraged the recently developed E-value to provide a measure of robustness of these results to unmeasured confounding [26], finding that any potential confounder not measured in our study would need to be associated with an odds ratio of at least 1.9–3.8 with the exposure and outcomes, independent of the measured confounders, to fully explain away the associations found, which can be regarded as unlikely in light of current knowledge. For example, obesity, which is a common and strong confounder for the association between wheezing and nGOR (and was therefore adjusted for in our analysis), has been shown in another study to have an odds ratio of 2.2, an effect larger than other measured confounders in that study [37]. We are therefore not aware of potential confounders (outside those measured in our study) that could have such a strong confounding effect, which further strengthens our conclusions.

However, a few methodological weaknesses also need to be noted. First, we had no objective measurement for nGOR. The questionnaire-based definition used has been utilised in previous studies on associations between nGOR and respiratory symptoms, and identifies participants with significant nGOR reasonably well [35, 38]. We also included data on nGOR medication use in our definition, which should decrease potential healthy user effects. Second, a minority of patients did not have PAP device data on compliance, so for them compliance was assessed using questionnaire data. However, the correlation between questionnaire data and PAP device data was acceptable, where both were available, and therefore any effects from this lack of objective PAP data are likely minimal. Also, the number of highly symptomatic patients at baseline with both nGOR and respiratory symptoms was too limited to allow more detailed subgroup analysis, and also limited the power for the mediation analysis. A study recruiting only OSA patients with respiratory symptoms and a high nGOR prevalence would allow more specific mechanistic analysis of these associations.

Conclusion

Our findings show that treating OSA patients with PAP decreases their nGOR and wheezing, and to a lesser extent decreases their productive cough. PAP treatment directly affects the presence of wheezing irrespective of changes in nGOR, but the PAP treatment effect on productive cough seems mainly to be mediated through diminished nGOR. For patients with OSA and productive cough, treatment modalities other than PAP may be needed, especially if nGOR is absent. However, for OSA patients with wheezing or nGOR, PAP treatment is likely to have a beneficial effect.

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Conflict of interest: All authors have nothing to disclose.

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