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Longitudinal associations between sleep disturbance and disease severity in patients with COPD

Faith S. Luyster^{1*} , Juan Wang², Frank C. Sciruba³ and Jessica Bon^{3,4}

Abstract

Background: Sleep disturbance is a common complaint among patients with chronic obstructive pulmonary disease (COPD). Studies examining the associations between sleep disturbance and COPD severity have primarily been cross-sectional and produced conflicting results. We extended previous research by investigating the bidirectional longitudinal associations between sleep disturbance and indicators of COPD severity including airway obstruction, dyspnea, health status, exercise capacity, hyperinflation, and diffusing capacity of the lung (DLCO).

Methods: We used longitudinal data from the COPD Specialized Center for Clinically Oriented Research (SCCOR) prospective cohort. One hundred fifty-seven patients with COPD (54.1% male, 66.3 ± 6.4 years) completed assessments at baseline and 2-year follow-up. Primary outcomes of interest were: sleep disturbance based on a single item from the Beck Depression Inventory; airflow obstruction, defined by FEV₁% predicted from spirometry; health status, as measured by the St. George's Respiratory Questionnaire; exercise capacity, as determined by walking distance (meters) during an incremental shuttle walk test; dyspnea, as measured by the modified Medical Research Council scale; DLCO, determined by single breath carbon monoxide diffusion; and hyperinflation, defined by residual volume from body plethysmography. Linear and logistic regression analyses were conducted, correcting for baseline outcome severity.

Results: After controlling for covariates of age, sex, race, body mass index, and smoking status, sleep disturbance was associated with worse health status at baseline. Using longitudinal follow-up data, greater disease severity including airflow obstruction, dyspnea, health status, exercise capacity, and DLCO independently predicted sleep disturbance at 2-year follow-up. Baseline sleep disturbance was not associated with subsequent disease severity.

Conclusions: Disease severity predicts future sleep disturbance in COPD patients. This suggests that COPD severity may be a risk factor for the development of sleep problems, and therefore better COPD control may be a preventative strategy for sleep disturbance.

Keywords: Sleep disturbance, Chronic obstructive pulmonary disease, Dyspnea, Exercise capacity

Introduction

Chronic obstructive pulmonary disease (COPD), an airway disease characterized by progressive airflow limitation that is not fully reversible, is one of the leading causes of morbidity and mortality globally (López-Campos et al. 2016). Disturbed sleep is a major complaint among patients with

COPD (Kauffman et al. 2014). Patients often report frequent nocturnal awakenings, poor sleep quality, and difficulties falling asleep (Ding et al. 2017; Omachi et al. 2012; Zeidler et al. 2018). Subjective sleep measures have been corroborated with actigraphic and polysomnographic assessments that demonstrate lower sleep efficiency and total sleep time in patients with COPD compared with controls (Nunes et al. 2013; Valipour et al. 2011).

Potential sources of sleep difficulties in COPD include smoking and psychiatric and medical comorbidities such

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as depression, anxiety, obstructive sleep apnea (OSA), restless legs syndrome (RLS), and pain (Budhiraja et al. 2015; McNicholas et al. 2013). Physiologic alterations in COPD that are accentuated during sleep including reduced airflow, ventilation/perfusion mismatch, and hypoventilation and associated hypoxemia and hypercapnia may lead to nocturnal arousals and symptoms including dyspnea, cough, and sputum production that disrupt sleep (Budhiraja et al. 2015; Kwon et al. 2009; McNicholas et al. 2013; Stephenson et al. 2015). Irrespective of the etiology, sleep disturbance has been shown to be a predictor of adverse health outcomes including COPD exacerbations and survival, thus suggesting that sleep may affect disease severity (Omachi et al. 2012; Shorofsky et al. 2019). The association between COPD severity and sleep disturbance is not clear. Indicators of disease severity including Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification, airway obstruction as measured by forced expiratory volume in 1 s (FEV_1), health status, and symptoms such as cough, wheezing, dyspnea, and frequent sputum production have been found to be associated with worse sleep quality and sleep disturbance (Chang et al. 2016; Hartman et al. 2015; Nunes et al. 2013; Omachi et al. 2012; Zeidler et al. 2018). However, other studies have found no associations between airflow obstruction severity and sleep disturbance (Geiger-Brown et al. 2015; Omachi et al. 2012; Zeidler et al. 2018). In addition to the above mentioned indicators of disease severity, exercise capacity is also an important marker of disease severity. The association between sleep disturbance and exercise capacity has received little attention (Vardar-Yagli et al. 2015; Zeidler et al. 2018).

The available literature examining the relationship between sleep disturbance and various indicators of COPD severity have reported conflicting results and have been cross-sectional, thus, it is unclear whether there may be a bi-directional relationship between sleep disturbance and disease severity in COPD. We used an established prospective longitudinal cohort of current and former smokers with COPD to examine cross-sectional and bi-directional longitudinal relationships between sleep disturbance and COPD severity. We hypothesized that (a) sleep disturbance at baseline would be associated with lower $FEV_1\%$ predicted, increased dyspnea and hyperinflation, and reduced health status, exercise capacity, and diffusing capacity of the lung (DLCO) at baseline, (b) sleep disturbance at baseline predicts worsening $FEV_1\%$ predicted, dyspnea, health status, hyperinflation, exercise capacity, and DLCO over 2 year follow-up and (c) $FEV_1\%$ predicted, dyspnea, health status, hyperinflation, exercise capacity, and DLCO at baseline predicts the presence of sleep disturbance at 2 year follow-up in patients with COPD.

Methods

Participants

The study population consisted of participants in the single-center, COPD Specialized Center for Clinically Oriented Research (SCCOR) cohort at the University of Pittsburgh. SCCOR participants were primarily recruited from the Pittsburgh Lung Screening Study cohort, a tobacco-exposed cohort with a range of obstructive lung disease severity. The inclusion criteria for SCCOR participants were current or former smoker, age ≥ 40 years, and a minimum 10-pack-year tobacco history at enrollment. The exclusion criteria for SCCOR participants were clinical or radiographic evidence of another pulmonary disease (e.g., interstitial lung disease), history of lung cancer or a new, suspicious nodule on CT scan, and body mass index (BMI) > 34 . For the current analyses, only participants who had COPD as defined by GOLD stage (FEV_1 /forced vital capacity (FVC) < 70) were included. A total of 426 participants from the SCCOR cohort had COPD. The present analyses were limited to those who had data available on the variables of interest at both baseline and 2 year follow-up ($N = 157$). The group with missing data due to inability to complete assessment or missed follow-up visit had a lower proportion of current smokers and had more severe COPD as indicated by greater use of supplemental oxygen, greater oral and inhaled corticosteroid use, higher frequency of GOLD stage 4 and Group D, lower $FEV_1\%$ predicted, exercise capacity, and DLCO, and worse dyspnea, health status, and hyperinflation than the group with data at both time points. The study was approved by the University of Pittsburgh Institutional Review Board and informed consent was obtained from all participants.

Measures

All study procedures were conducted at baseline and at 2-year follow-up. Questionnaires were administered to gather data on demographics, smoking, self-reported medical and medication history, and current use of supplemental oxygen. Participants were categorized into groups based on the 2017 GOLD "ABCD" assessment tool (Vogelmeier et al. 2017).

The Beck Depression Inventory-II (BDI-II) is a 21-item measure that assesses depressive symptoms using a 4-point scale (0–3) with a maximum total score of 63 (Beck et al. 1996; Dozois et al. 1998). Depressive symptom categories include minimal (0–13), mild (14–19), moderate (20–28), and severe (29–63). A single item from the Beck Depression Inventory-II was used to assess sleep disturbance. Responses include: 0 = I can sleep as well as usual, 1 = I don't sleep as well as I used to, 2 = I wake up 1–2 h earlier than I used to and find it hard to get back to sleep, 3 = I wake up several hours earlier

than I used to and cannot get back to sleep. The variable was dichotomized into 0 = “no disturbed sleep” and 1 = “disturbed sleep”, which encompassed responses 1–3.

The incremental shuttle walk test (ISWT) is a well validated test to assess exercise capacity in COPD patients (Singh et al. 1992; Singh et al. 1994). Participants walk on a level, ten meter course at a pace dictated by audio signals, incrementally increasing in frequency each minute, until either the participant is too breathless to maintain regular speed, is unable to complete the ten meter shuttle in the allowed time, or has walked for 20 min. Exercise capacity is defined by walking distance (meters) during the ISWT.

The modified Medical Research Council (mMRC) scale measures severity of breathlessness related to day-to-day activities on a scale from 0 (no breathlessness only with strenuous exercise) to 4 (too breathless to leave house or breathless when dressing) (Bestall et al. 1999). The St. George’s Respiratory Questionnaire (SGRQ) is a 50-item measure assessing health status within three domains: symptoms, activity, and impact (Jones et al. 1991). The total score, ranges from 0 to 100, with higher scores indicating worse health status.

Pre- and post-bronchodilator spirometry was performed according to the American Thoracic Society guidelines (Miller et al. 2005). FEV₁, FVC, ratio of FEV₁/FVC were recorded. Body plethysmography and single breath carbon monoxide diffusion were performed according to the recommendations of the American Thoracic Society/European Respiratory Society Task Force on standardization of lung function testing (Macintyre et al. 2005; Wanger et al. 2005).

Statistical analysis

Descriptive statistics including frequency (%) for categorical variables and mean \pm SD for continuous variables were computed. Comparisons of variables between those with and those without sleep disturbance were performed using Student t test or χ^2 test. To evaluate the cross-sectional associations between sleep disturbance and indicators of COPD severity including FEV₁% predicted (airflow obstruction), mMRC (dyspnea), SGRQ (health status), ISWT distance (exercise capacity), residual volume ((RV), hyperinflation), and DLCO, we performed linear regression analyses on the baseline data. The following covariates were included in the regression analyses: age, sex, race, BMI, and smoking status. To assess whether the presence of sleep disturbance at baseline predicted COPD severity after 2 years of follow-up, we used separate linear regression analyses. We corrected for baseline value of the respective outcome variable in the model along with the above stated covariates. To evaluate the inverse temporal relationship between these variables, we performed a logistic regression

analysis with the presence of sleep disturbance (0 = sleep disturbance not present, 1 = sleep disturbance present) as the dependent variable, and either FEV₁% predicted, mMRC, SGRQ, ISWT distance, residual volume, or hyperinflation at baseline as the independent variables. A two-sided *P* value < .05 was set for statistical significance. All analyses were performed with SPSS 25 for Windows (IBM Corp., Armonk, NY).

Results

Participant characteristics

Table 1 presents the baseline characteristics of participants. The mean age was 66.3 years, with a roughly equal sex distribution (Table 1). The majority of participants were former smokers with mild to moderate COPD according to GOLD stage classification. Participants without sleep disturbance had higher BMI than those with sleep disturbance (28.2 ± 4.2 vs. 26.9 ± 4.0 , $p < 0.05$). No significant differences in the other baseline characteristics were found between those with and without disturbed sleep.

The prevalence of sleep disturbance at baseline was 47%. The mean FEV₁% predicted at baseline was 69.3 ± 18.4 , mean mMRC 1.1 ± 0.9 , mean SGRQ 25.0 ± 17.2 , and ISWT distance in meters 399.6 ± 146.71 . At follow-up, the prevalence of sleep disturbance was 53.5%. The mean FEV₁% predicted at follow-up was 68.8 ± 18.8 , mean mMRC 1.3 ± 1.1 , mean SGRQ 27.6 ± 17.4 , and ISWT distance 381.3 ± 140.9 m. Thus, the frequency of sleep disturbance increased and dyspnea, health status, and exercise capacity worsened slightly over the 2-year follow-up. Over 2-year follow-up, 8 (5.1%) reported having an unscheduled emergency room visit and 5 (3.2%) reported having a hospitalization due to an acute COPD exacerbation.

Cross-sectional associations between sleep disturbance and airflow obstruction, exercise capacity, health status, dyspnea, DLCO, and hyperinflation

At baseline, mean SGRQ was higher in participants with sleep disturbance compared to those without sleep disturbance, indicating worse health status (Table 1). In contrast, FEV₁% predicted, dyspnea, ISWT distance, RV, and DLCO were similar in those with and without sleep disturbance. After adjustment for covariates including age, sex, race, BMI, and smoking status, the association between baseline SGRQ and presence of sleep disturbance at baseline was significant (β [95% CI] = 0.22 [2.08, 13.21], $p < 0.01$) (Table 2).

Longitudinal associations between sleep disturbance and airflow obstruction, exercise capacity, health status, dyspnea, DLCO, and hyperinflation

Baseline sleep disturbance was not associated with FEV₁% predicted (β [95% CI] = 0.03 [-1.42, 3.73], $p = 0.38$),

Table 1 Participant characteristics at baseline according to sleep disturbance

	Total (N = 157)	Sleep disturbance (n = 74)	No sleep disturbance (n = 83)	Unadjusted <i>p</i> -value
Age, year, mean (SD)	66.3 (6.4)	66.5 (6.2)	66.1 (6.5)	0.67
Sex, male, n (%)	85 (54.1%)	44 (59.4%)	41 (49.4%)	0.21
White, n (%)	151 (96.2%)	70 (94.6%)	81 (97.5%)	0.33
BMI, mean (SD)	27.6 (4.1)	26.9 (4.0)	28.2 (4.2)	0.04
Pack years, mean (SD)	64.8 (34.1)	66.9 (34.2)	62.9 (34.1)	0.46
Current smoker, n (%)	62 (39.5%)	35 (47.3%)	27 (32.5%)	0.06
Supplemental oxygen use, n (%)	9 (5.7%)	5 (6.8%)	4 (4.8%)	0.60
ICS use, n (%)	8 (5.1%)	6 (8.1%)	2 (2.4%)	0.11
OCS use, ^a n (%)	40 (25.5%)	20 (27.0%)	20 (24.1%)	0.67
GOLD stage, n (%)				
Stage 1	46 (29.3%)	20 (27.0%)	26 (31.3%)	0.77
Stage 2	87 (55.4%)	42 (63.5%)	45 (54.2%)	
Stage 3	21 (13.4%)	10 (13.5%)	11 (13.3%)	
Stage 4	3 (1.9%)	2 (2.7%)	1 (1.2%)	
GOLD ABCD group, n (%)				
Group A	106 (67.5%)	47 (63.5%)	59 (71.1%)	0.64
Group B	26 (16.6%)	13 (17.6%)	13 (15.7%)	
Group C	14 (8.9%)	7 (9.5%)	7 (8.4%)	
Group D	11 (7.0%)	7 (9.5%)	4 (4.8%)	
Comorbidities, n (%)				
Diabetes	9 (5.7%)	3 (4.2%)	6 (7.2%)	0.42
Hyperlipidemia	84 (53.5%)	39 (53.4%)	45 (55.6%)	0.79
Cancer	25 (15.9%)	8 (10.8%)	17 (20.5%)	0.10
Asthma	17 (10.8%)	30 (40.5%)	20 (24.7%)	0.32
GERD	50 (31.8%)	10 (13.9%)	7 (8.8%)	0.04
Bronchitis	75 (47.8%)	42 (60.0%)	33 (42.3%)	0.03
BDI-II category, n (%)				
Minimal/Mild	151 (96.2%)	69 (93.2%)	82 (98.8%)	0.07
Moderate/ Severe	6 (3.8%)	5 (6.8%)	1 (1.2%)	0.56
FEV ₁ pp., mean (SD)	69.3 (18.4)	8.4 (19.0)	70.2 (18.1)	0.40
mMRC, mean (SD)	1.1 (0.9)	1.1 (1.1)	0.9 (0.9)	0.005
SGRQ, mean (SD)	25.0 (17.2)	29.0 (18.1)	21.4 (15.6)	0.72
ISWT distance (m), mean (SD)	399.6 (146.7)	394.9 (141.8)	403.6 (152.0)	0.58
RV pp., mean (SD)	138.4 (35.9)	140.1 (34.8)	136.8 (37.0)	0.99
RV/TLC, mean (SD)	0.49 (0.10)	0.49 (0.10)	0.49 (0.10)	0.15
DLCO pp., mean (SD)	66.9 (19.8)	64.5 (21.6)	69.1 (18.0)	0.56

BDI-II Beck Depression Inventory-II, *BMI* body mass index, *FEV₁ pp* forced expiratory volume in 1 s percent predicted, *GERD* gastroesophageal reflux disease, *SD* standard deviation, *mMRC* modified Medical Research Council scale, *SGRQ* St. George's Respiratory Questionnaire, *ISWT* = Incremental shuttle walk test, *RV pp* residual capacity percent predicted, *DLCO pp* diffusion capacity for carbon monoxide percent predicted

^aOral steroid use, temporary short-term use in past 6 months

mMRC (β [95% CI] = 0.11 [- 0.05, 0.55], $p = 0.10$), SGRQ (β [95% CI] = 0.01 [- 2.68, 3.51], $p = 0.79$), ISWT distance (β [95% CI] = - 0.02 [- 31.63, 23.28], $p = 0.76$), RV (β [95% CI] = 0.03 [- 5.08, 9.62], $p = 0.54$), or DLCO (β [95% CI] = - 0.06 [- 5.32, 0.37], $p = 0.09$) at 2-year follow-up, after

correcting the model for baseline values of these independent variables and covariates including age, sex, race, BMI, and smoking status (Table 3). When looking at the reverse relationships, baseline mMRC (OR [95% CI] = 1.77 [1.16, 2.68, $p < 0.01$]), SGRQ (OR [95% CI] = 1.04 [1.01,

Table 2 Linear regression analysis with presence of sleep disturbance at baseline as independent variable and COPD severity at baseline as dependent variable

	Dependent Variable			Dependent Variable			Dependent Variable			Dependent Variable		
	Baseline FEV ₁ pp	Baseline mMRC	Baseline SGRQ	Baseline ISWT distance	RV pp	DLCO pp	β	95% CI	p-value	β	95% CI	p-value
Model 1:												
Baseline SD	-0.05 (-7.35, 2.55)	0.34 (0.07, 0.61)	0.40 (0.22, 0.58)	0.005 (-56.29, 38.98)	0.72 (0.05, 1.39)	-0.11 (-10.77, 1.71)	0.34	(-0.18, 0.45)	0.005	(-8.17, 14.59)	0.57	0.15
Model 2:												
Baseline SD	-0.04 (-6.34, 2.05)	0.32 (0.07, 0.57)	0.42 (0.22, 0.62)	-0.10 (-72.10, 12.12)	0.16 (-0.02, 0.32)	-0.09 (-9.68, 2.49)	0.32	(-0.19, 0.46)	0.007	(-12.30, 10.13)	0.85	0.25
Age	0.31 (0.82, 1.39)	<0.001 (0.11, 0.51)	0.17 (-0.01, 0.34)	-0.35 (-11.20, -4.68)	<0.001 (-0.15, 0.15)	0.02 (-0.41, 0.53)	<0.001	(-0.01, -0.04)	0.87	(-1.70, 0.05)	0.07	0.80
Sex	0.02 (-3.27, 5.12)	0.67 (0.09, 1.25)	0.27 (-0.14, 0.50)	-0.34 (-140.02, -56.77)	<0.001 (-0.24, 0.24)	-0.09 (-9.67, 2.47)	0.67	(-0.14, 0.50)	0.40	(-28.44, -6.06)	0.003	0.24
Race	-0.04 (-15.04, 5.11)	0.33 (0.12, 0.54)	0.12 (-0.18, 0.51)	-0.04 (-136.17, 80.11)	0.61 (0.07, 1.15)	-0.10 (-25.96, 5.96)	0.33	(-0.18, 0.51)	0.12	(-16.46, 42.30)	0.39	0.22
BMI	0.21 (0.70, 1.54)	<0.001 (0.07, 0.35)	0.44 (-0.06, -0.03)	-0.17 (-11.55, -0.90)	0.02 (-0.21, 0.17)	0.34 (0.86, 2.38)	<0.001	(-0.06, -0.03)	0.72	(-3.19, -0.38)	0.01	<0.001
Smoking status	-0.40 (-28.39, -18.82)	0.35 (0.10, 0.60)	0.24 (-0.14, 0.53)	-0.10 (-74.06, 13.69)	0.18 (-0.13, 0.18)	-0.19 (-13.87, -1.27)	0.35	(-0.14, 0.53)	0.16	(-12.34, 10.57)	0.90	0.02

Note: FEV₁ pp = forced expiratory volume in 1 s percent predicted, mMRC = modified Medical Research Council scale, SGRQ = St. George's Respiratory Questionnaire, ISWT = Incremental shuttle walk test, β = standardized regression coefficient, 95% CI = 95% confidence interval, SD = sleep disturbance, BMI = body mass index, RV pp = residual capacity percent predicted, DLCO pp = diffusion capacity for carbon monoxide percent predicted

Table 3 Linear regression analysis with presence of sleep disturbance as independent variable and COPD severity at 2-year follow-up as dependent variable

Independent variable	Dependent Variable																										
	2 yr FEV ₁ % pp				2 yr mMRC				2 yr SGRQ				2 yr ISWT distance				2 yr RV pp				2 yr DLCO pp						
	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value			
Model 1:																											
Baseline SD	-0.02	(-6.86, 5.04)	0.76	0.12	(-0.09, 0.62)	0.14	0.18	(0.84, 11.66)	0.02																		
Model 2:																											
Baseline SD	0.03	(-1.42, 3.73)	0.38	0.11	(-0.05, 0.55)	0.10	0.01	(-2.68, 3.51)	0.79																		
Baseline DV	0.91	(0.86, 0.99)	<0.001	0.57	(0.49, 0.80)	<0.001	0.85	(0.77, 0.94)	<0.001	0.80	(0.68, 0.91)	<0.001	0.79	(0.72, 0.94)	<0.001	0.89	(0.80, 0.95)	<0.001	0.89	(0.80, 0.95)	<0.001	0.89	(0.80, 0.95)	<0.001	0.89	(0.80, 0.95)	<0.001
Age	-0.03	(-0.28, 0.16)	0.46	-0.06	(-0.03, 0.01)	0.34	-0.03	(-0.32, 0.15)	0.47	-0.13	(-5.20, -0.69)	0.01	-0.01	(-0.63, 0.52)	0.85	-0.05	(-0.36, 0.08)	0.20	-0.05	(-0.36, 0.08)	0.20	-0.05	(-0.36, 0.08)	0.20	-0.05	(-0.36, 0.08)	0.20
Sex	0.01	(-2.27, 2.86)	0.82	0.02	(-0.26, 0.35)	0.77	0.00	(-2.90, 3.14)	0.94	-0.02	(-35.08, 24.40)	0.72	-0.03	(-10.16, 4.96)	0.50	-0.05	(-4.95, 0.71)	0.14	-0.05	(-4.95, 0.71)	0.14	-0.05	(-4.95, 0.71)	0.14	-0.05	(-4.95, 0.71)	0.14
Race	-0.07	(-13.89, -0.35)	0.04	0.02	(-0.71, 0.88)	0.82	0.02	(-6.42, 9.47)	0.71	-0.06	(-128.69, 30.14)	0.22	0.01	(-17.81, 20.61)	0.89	-0.03	(-10.04, 4.90)	0.50	-0.03	(-10.04, 4.90)	0.50	-0.03	(-10.04, 4.90)	0.50	-0.03	(-10.04, 4.90)	0.50
BMI	-0.00	(-0.33, 0.32)	0.97	0.12	(-0.00, 0.07)	0.08	0.03	(-0.24, 0.52)	0.48	0.03	(-2.72, 4.59)	0.61	-0.03	(-1.23, 0.66)	0.55	-0.01	(-0.42, 0.34)	0.84	-0.01	(-0.42, 0.34)	0.84	-0.01	(-0.42, 0.34)	0.84	-0.01	(-0.42, 0.34)	0.84
Smoking status	0.03	(-1.42, 3.98)	0.35	0.07	(-0.15, 0.47)	0.31	0.10	(0.38, 6.64)	0.03	0.04	(-17.84, 39.32)	0.46	-0.06	(-12.24, 3.01)	0.23	0.01	(-2.55, 3.46)	0.76	0.01	(-2.55, 3.46)	0.76	0.01	(-2.55, 3.46)	0.76	0.01	(-2.55, 3.46)	0.76

Note: FEV₁, pp. = forced expiratory volume in 1 s percent predicted, mMRC = modified Medical Research Council scale, SGRQ = St. George's Respiratory Questionnaire, ISWT = Incremental shuttle walk test, β = standardized regression coefficient, 95% CI = 95% confidence interval, SD = sleep disturbance, DV = dependent variable, BMI = body mass index, RV pp. = residual capacity percent predicted, DLCO pp. = diffusion capacity for carbon monoxide percent predicted

1.06], $p < 0.01$), ISWT distance (OR [95% CI] = 0.99 [0.99, 1.00], $p < 0.05$), and DLCO (OR [95%CI] = 0.98 [0.96, 0.99], $p = 0.03$) were significantly associated with the presence of sleep disturbance at 2 years follow-up (Table 4). The association between baseline FEV₁% predicted and presence of sleep disturbance at follow-up approached significance (OR [95%CI] = 0.98 [0.96, 1.00], $p = 0.05$). RV at baseline was not significantly associated with presence of sleep disturbance at follow-up.

Discussion

In this study, we examined the cross-sectional and bidirectional longitudinal relationships between sleep disturbance and indicators of disease severity in a cohort of current and former smokers with COPD. Cross-sectional analyses revealed a significant association between sleep disturbance and health status but no significant associations between sleep disturbance and airflow obstruction, dyspnea, exercise capacity, hyperinflation, or DLCO. Baseline sleep disturbance was not a predictor of the disease severity indicators at 2-year follow-up, whereas airflow obstruction, dyspnea, health status, exercise capacity, and DLCO at baseline were predictors of sleep disturbance at follow-up.

A significant relationship between sleep disturbance and health status at baseline was found, yet the other indicators of COPD severity were not associated with sleep disturbance. These findings are in broad agreement with prior cross-sectional studies, which have demonstrated associations between sleep quality and health status (Lee et al. 2019; Scharf et al. 2011; Zeidler et al. 2018), but no associations with airflow obstruction or exercise capacity (Geiger-Brown et al. 2015; Omachi et al. 2012; Vardar-Yagli et al. 2015; Zeidler et al. 2018). However, an association between lower sleep efficiency and increased severity of hyperinflation was reported in a sample of

patients with COPD and obstructive sleep apnea (Kwon et al. 2009). Our findings suggest that that sleep disturbance may be more strongly linked to health status than these other markers of disease severity.

We found that sleep disturbance did not predict dyspnea, health status, airflow obstruction, exercise capacity, hyperinflation, or DLCO at follow-up after correction for baseline outcome severity. This is in contrast to prior studies in which poor sleep independently predicted subsequent exacerbations up to 18 months later suggesting that sleep disturbance is a risk factor for poor outcomes in COPD (Omachi et al. 2012; Shorofsky et al. 2019). There are several potential mechanisms by which sleep disturbance could contribute to worsening COPD. Poor sleep may affect immune function thus increasing susceptibility to infections (Majde and Krueger 2005; Veeramachaneni and Sethi 2006), accentuate systematic inflammation (Dumaine and Ashley 2015; MacNee 2013), lead to impaired cognitive function and resultant medication nonadherence (Fortier-Brochu et al. 2012; Riegel and Weaver 2009), and could be a manifestation of untreated OSA (Marin et al. 2010), all of which can worsen COPD control. The lack of association between sleep disturbance and disease severity in the current study could be explained by the measure used to assess sleep disturbance. We used a single item from the BDI. Previous studies examining associations between sleep and COPD outcomes have primarily used validated sleep instruments (e.g., Pittsburgh Sleep Quality Index), therefore use of validated subjective and objective measures of sleep may have yielded differing results. Furthermore, our cohort mostly had mild to moderate COPD with infrequent exacerbations, thus association may have been found in a cohort with a higher rate of acute exacerbations.

We found that baseline dyspnea, health status, airflow obstruction, exercise capacity, and DLCO predicted occurrence of sleep disturbance at 2 year follow-up. Reduced airflow could affect sleep due to nocturnal arousals associated with hypoxemia and hypercapnia caused by accentuated hypoventilation, particularly during rapid eye movement (REM) sleep (Budhiraja et al. 2015). Hypoxemia in individuals with marked diffusion limitation may contribute to nocturnal dyspnea which can be particularly disruptive to sleep. Reduced exercise capacity may be a marker of lung disease severity, but may also be reflective of comorbidities such as cardiovascular disease or obstructive sleep apnea, which can lead to sleep disturbance (Lavie et al. 2015; Mendelson et al. 2018). Depression and anxiety associated with dyspnea and reduced exercise capacity could also lead to sleep disturbance (Al-shair et al. 2009; Chavannes et al. 2005; Kim et al. 2014; Shackell et al. 2007; Suh et al. 2013).

Findings from this study should be interpreted in consideration of certain limitations. As previously stated,

Table 4 Logistic regression analyses with COPD severity at baseline as independent variable and sleep disturbance at 2-year follow-up as dependent variable

	OR (95% CI)	p-value
FEV ₁ pp	0.98 (0.96, 1.00)	0.05
mMRC	1.77 (1.16, 2.68)	0.008
SGRQ	1.04 (1.01, 1.06)	0.004
ISWT distance	0.99 (0.99, 1.00)	0.04
RV pp	1.01 (0.99, 1.02)	0.38
DLCO pp	0.98 (0.96, 0.99)	0.03

Note: All analyses control for age sex, race, body mass index, and smoking. Each COPD severity variable above was used as an independent variable in its own multivariable logistic regression analysis. FEV₁ pp, forced expiratory volume in 1 s percent predicted, mMRC modified Medical Research Council scale, SGRQ St. George’s Respiratory Questionnaire, ISWT Incremental shuttle walk test, OR odds ratio, 95% CI 95% confidence interval, RV pp, residual capacity percent predicted, DLCO pp, diffusion capacity for carbon monoxide percent predicted

sleep disturbance was not assessed by a validated sleep questionnaire. Furthermore, objective assessment of sleep such as polysomnography was not conducted, thus prohibiting us from understanding the etiology of the sleep disturbance which could have in part been related to sleep disordered breathing. We excluded individuals with missing data at follow-up who were those with more severe COPD, which limits generalizability of the results to those with greater disease severity.

Conclusions

We found airflow obstruction, dyspnea, health status, exercise capacity, and DLCO predict future sleep disturbance in individuals with COPD. Future research should utilize validated sleep assessments to further our understanding of the directionality of the relationship between sleep disturbance and COPD severity. This study suggests that COPD severity may be a risk factor for the development of sleep problems, and therefore better COPD control may be a preventative strategy for sleep disturbance.

Abbreviations

BDI-II: Beck Depression Inventory-II; BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; DLCO: Diffusing Capacity of the Lung; FEV₁: Forced Expiratory Volume in One Second; FVC: Forced Vital Capacity; GERD: Gastroesophageal Reflux Disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease; ISWT: Incremental Shuttle Walk Test; mMRC: Modified Medical Research Council scale; REM: Rapid Eye Movement; RV: Residual Volume; SCCOR: Specialized Center For Clinically Oriented Research; SGRQ: St. George's Respiratory Questionnaire

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Authors' contributions

FSL conceptualized the idea for the manuscript, analyzed and interpreted the data as well as wrote the manuscript. JW played a role in the interpretation of results and manuscript editing and revision. FCS had a role in the study design, data collection, interpretation of results, and manuscript revision. JB had a role in the study design, data collection, interpretation of results and manuscript editing and revision. All authors read and approved the final manuscript.

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Availability of data and materials

The raw data on which results in the current study are based may be requested from the corresponding author upon reasonable request.

Ethics approval and consent to participate

The study was approved by the Institutional Review Board at the University of Pittsburgh prior to study initiation. Informed consent to participate was obtained from each participant prior to study enrollment.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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