Objective evaluation of nocturnal sleep impairment in patients with COPD and its association with daytime physical activity

Gabriele Spina[1,2] MSc, Martijn A. Spruit[3,4] PhD, Jennifer Alison[5,6] PhD, Roberto P. Benzo[7] MD, Peter M. A. Calverley[8] MD, Christian F. Clarenbach[9] MD, Richard W. Costello[10] MD, David Donaire-Gonzalez[11,12,13] PhD, Selina Dürr[14] MSc, Judith Garcia-Aymerich[11,12,13] MD, Arnoldus J. R. van Gestel[9] MD, Marco Gramm[15] UID, Nidia A. Hernandes[16] PhD, Kylie Hill[17] PhD, Nicholas S. Hopkinson[18] MD, Diana Jarreta[19] BSc, Malcolm Kohler[9] MD, Anne M. Kirsten[15] MD, Jörg D. Leuppi[14] MD, Helgo Magnussen[15] MD, François Maltais[20] MD, William D-C. Man[18] MD, Zoe J. McKeough[5] PhD, Rafael Mesquita[3,21] MSc, David Miedinger[14] MD, Fabio Pitta[16] PhD, Sally J. Singh[22] PhD, Frank W. J. M. Smeenk[23] MD, Ruth Tal-Singer[24] PhD, Barbara Vagaggini[25] MD, Benjamin Waschki[15] MD, Henrik Watz[15] MD, Emiel F. M. Wouters[3,21] MD, Stefanie Zogg[14] MSc, Albertus C. den Brinker[2] PhD.

[1]Department of Signal Processing Systems, Technische Universiteit Eindhoven, Eindhoven, The Netherlands.

[2]Data Science Group, Philips Research, Eindhoven, The Netherlands.

[3]Department of Research & Education, Center of expertise for chronic organ failure + (CIRO+), Horn, The Netherlands.

[4]REVAL - Rehabilitation Research Center, BIOMED - Biomedical Research Institute, Faculty of Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium.

[5]Clinical and Rehabilitation Sciences, The University of Sydney, Sydney, NSW, Australia.

[6]Physiotherapy Department, Royal Prince Alfred Hospital, Sydney, NSW, Australia.

[7]Mindful Breathing Laboratory, Mayo Clinic, Rochester, MN, United States of America.

[8]School of Ageing and Chronic Disease, University Hospital Aintree, Liverpool, United Kingdom.

[9]Pulmonary Division, University Hospital of Zurich, Zurich, Switzerland.

[10]Department of Respiratory Medicine, Beaumont Hospital, Dublin, Ireland.

[11]Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain.

[12]CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain.

[13]Universitat Pompeu Fabra (UPF), Barcelona, Spain.

[14]Medical University Clinic, Cantonal Hospital Baselland, Liestal and Medical Faculty, University of Basel, Basel, Switzerland.

[15]Pulmonary Research Institute at Lung Clinic Grosshansdorf, Airway Research Center North, Member of the German Centre for Lung Research, Grosshansdorf, Germany.

[16]Laboratory of Research in Respiratory Physiotherapy, Department of Physiotherapy, State University of Londrina (UEL), Londrina, Brazil.

[17]School of Physiotherapy and Exercise Science, Curtin University, Perth, WA, Australia.

[18]NIHR Respiratory Biomedical Research Unit, Royal Brompton & Harefield NHS Foundation Trust and Imperial College, London, United Kingdom.

[19] AstraZeneca, Barcelona, Spain

[20]Centre de recherche, Institut Universitaire de cardiologie et de pneumologie de Québec, 2725 Chemin Ste-Foy Québec, Université Laval, Québec G1V 4G5, Canada.

[21]Department of Respiratory Medicine, Maastricht University Medical Center+ (MUMC+), Maastricht, The Netherlands.

[22]Centre for Exercise and Rehabilitation Science, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom.

[23]Department of Respiratory Medicine, Catharina Hospital, Eindhoven, The Netherlands.

[24]GSK R&D, King of Prussia, PA, United States of America.

[25]Cardio-Thoracic and Vascular Department, University of Pisa, Pisa, Italy.

The authors declare that there are no conflicts of interest.

Correspondence:

Gabriele Spina, MSc,

Department of Electrical Engineering, Signal Processing SystemsGroup;

Technische Universiteit Eindhoven, Flux-7.60, PO Box 513, 5600 MB Eindhoven, The Netherlands;

Telephone number: +31 628460517;

Email: g.spina@tue.nl

Summary

Background Sleep disturbances are common in patients with chronic obstructive pulmonary disease (COPD) with a considerable negative impact on their quality of life. However, factors associated with objective sleep impairment have not been investigated before in a large patient population nor has the association between sleep impairment and the ability to engage in physical activity on a day-to-day basis been studied.

Methods Data were analyzed from 932 patients with COPD (65·5% male, 66·4±8·3 years, FEV_1 % predicted = 50·8±20·5). Participants had sleep and physical activity continuously monitored in their home environment using a multi-sensor activity monitor for a median of six days. The main factors associated with sleep impairment were identified using linear mixed effects models to account for different sources of variance in the data. The association of nocturnal sleep impairment with patients' subsequent physical activity, and daytime sleep, was investigated.

Findings Objectively measured sleep impairment was greater in patients with worse airflow limitation and worse exertional dyspnea. Nights characterized by more sleeping bouts (>2), shorter sleeping bouts (<225 minutes), lower sleep efficiency (<91%) and more time spent awake after sleep onset (>57 minutes) were followed by days with significantly lower levels of physical activity.

Interpretation There is a clear relationship between measures of COPD patients sleep and the amount of activity they undertake during the waking day. Identifying groups with specific sleep characteristics may be useful information when designing physical activity enhancing interventions with realistic goals for this population.

Funding iCare4COPD Project of Agentschap NL, foundations "Gottfried und Julia Bangerter-Rhyner-Stiftung", "Freiwillige Akademische Gesellschaft Basel" and "Forschungsfonds der Universität Basel".

Introduction

Chronic obstructive pulmonary disease (COPD) is a global health problem and is currently the third leading cause of death worldwide.[1] In addition to progressive chronic airflow limitation, patients with COPD commonly have multiple extrapulmonary effects and comorbidities, which are associated with physical inactivity.[2] Although there is general agreement about the need to assess and improve physical activity in people with COPD, the factors associated with patient's capability to engage in physical activity are not well established, which may limit the impact of physical activity enhancement interventions.[3]

Sleep disturbance, such as sleep fragmentation during the night, is common in patients with COPD,[4] and is a major complaint after dyspnea and fatigue.[5] Despite the high prevalence of disturbed sleep in COPD, nighttime symptoms are often underestimated and are not a focus of current disease management.[4]

Nocturnal sleep has been shown to be markedly impaired in patients with COPD compared to controls.[6] However, there is scant and discordant information on whether objectively assessed sleep disturbances worsen as the severity of dyspnea and airflow limitation increases.[6,7] Therefore, more data and in depth analysis are needed for a better understanding of the factors associated with sleep impairment in patients with COPD.
In healthy individuals, better sleep quality has been associated with higher exercise levels.[8,9] Even though several studies have investigated the daytime consequences of reduced sleep quality in patients with COPD like fatigue, psychiatric problems and impaired quality of life,[10,11] no published study has objectively investigated the association of disturbed sleep with subsequent physical activity in this patient population.

In this study, data were pooled from different studies resulting in a large sample of patients with mild to very severe COPD who had extended objective measures of sleep and physical activity during daily life assessed using a multi-sensor activity monitor. These data were used to: (1) provide insight into the relationship between objectively determined sleep measures and disease severity, dyspnea, gender, and day group (i.e. weekdays vs weekends); and (2) investigate whether there was an association between objectively assessed sleep measures and next day activity level.
Our hypotheses were that: patients with more severe COPD defined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria and higher Modified Medical Research Council (MMRC) dyspnea score would have more objectively measured sleep disturbances, and that nights of impaired sleep would be followed by days characterized by lower levels of physical activity.

Material and methods

Participants

In this retrospective, cross-sectional study, data were pooled from previous studies (appendix pp 5-7) as assessed by the SenseWear Armband or SenseWear Mini Armband activity monitors (BodyMedia Inc., Pittsburgh, PA, USA). Data collected across ten countries from 1384 patients diagnosed with mild to very severe COPD defined spirometrically were considered for analysis. Participants were included if they had COPD with a post-bronchodilator ratio of forced expiratory volume in the first second (FEV_1) to forced vital capacity (FVC) < 0·70 and they were clinically stable (i.e., stable shortness of breath and sputum production). We report baseline data recorded before any specific interventions were undertaken. The data collection was conducted in accordance with the declaration of Helsinki and approved by ethics committees at each of the participating centers, according to local regulations. Written informed consent was provided by all participants.

Sensor measurements

Physical activity levels and sleep were assessed during daily life with the SenseWear Armband devices that include an accelerometer with different physiological sensors.[12,13] Data were sampled at one minute intervals and, together with demographic characteristics, were used to estimate metabolic equivalent of task (MET) using proprietary algorithms developed by the manufacturer. The use of multisensory data in combination with pattern recognition algorithms ensured that the MET estimation was insensitive to noise and random motion artefacts.[14] METs data were divided into activity intensity levels using the thresholds proposed by the American College of Sports Medicine: very light intensity, < 2·0 METs; light intensity, 2·0 to 2·9 METs; and moderate-to-vigorous intensity, ≥ 3·0 METs.[15] For each minute, the device recorded steps count, information about the sleeping status of a patient (0=awake, 1=sleeping), and posture (0=lying down, 1=not lying down).

Data recordings

Study participants wore the sensor on the upper arm both during daytime and nighttime so that continuous, real-life activities were recorded. Participants who wore the device for at least 22 hours per day, with a minimum of four assessed days (two weekdays + Saturday + Sunday) were included.[13] Time in bed and time out of bed were derived from the minutes coded by the activity monitor as “sleeping” and “lying down” using a custom-made algorithm (appendix pp 8-15). Based on these data the following nighttime and daytime sleep measures were derived: total night sleeping time, number of nocturnal sleeping bouts, duration of nocturnal sleeping bouts, sleep efficiency, wake after sleep onset, total day sleeping time, number of daytime sleeping bouts, and average duration of daytime sleeping bouts. In this study, “sleep quality” is used to refer to the collection of these sleep measures which definition is presented in Table 1.

Sleeping bouts were defined as consecutive minutes marked by the sensor as sleeping. As physical activity measures, the number of steps performed during day time and the time spent in very light, light and moderate-to-vigorous activities were computed for each assessed day. Participants who did not have their sleep regularly distributed during nighttime or who had less than four hours of time in bed were excluded to minimize the inclusion of shift-workers and to reduce the impact of sleep morbidities such as insomnia.

Table 1 Nocturnal and daytime sleep measures derived from actigraphy data.

Variable name	Abbreviation	Description
Total Night Sleeping Time	TNST	Total night sleeping time is calculated as the sum of all minutes scored as sleep during time in bed.
Number of Nocturnal Sleeping Bouts	NNSB	Number of nocturnal sleeping bouts during time in bed. A higher NNSB indicates more fragmented sleep.
Duration of Nocturnal Sleeping Bouts	DNSB	Average duration of nocturnal sleeping bouts during time in bed. A higher DNSB indicates longer sleeping bouts, and, in turn less nocturnal sleeping disturbances.
Sleep efficiency	Seff	Sleep efficiency defined as the ratio of TNST and time in bed.
Wake After Sleep Onset	WASO	Time spent awake during time in bed after the first nocturnal sleep onset.
Total Day Sleeping Time	TDST	Total day sleeping time defined as the total time spent asleep during the out of bed period.
Number of Daytime Sleeping Bouts	NDSB	Number of daytime sleeping bouts indicates how many naps a patient takes during the day.
Duration of Daytime Sleeping Bouts	DDSB	Average duration of daytime sleeping bouts during the day. A higher DDSB indicates longer naps.

Statistical analysis

Linear mixed-effect models were used to study: (i) which factors influenced sleep quality measures, and (ii) whether and to what extent sleep quality measures were associated with subsequent daily physical activity levels and daytime sleep in patients with COPD.

To account for repeated measurements, we used random effects on two levels. On the highest level, we included a random intercept per patient. The second level, within patients, had a random intercept for each day group (weekdays vs. weekends). The residuals then accounted for the differences between days within the same day group.

To construct the models standard statistical packages were used (details can be found in appendix p 17). Least squares means (LS-means) and differences of LS-means of the fixed effects were calculated to present the results. Degrees of freedom and *p*-values for significant differences (significant if $p<0{\cdot}05$) were computed using Satterthwaite's approximation.[16] Comparisons of demographic and clinical characteristics between included and excluded patients were evaluated by Mann-Whitney U-test for continuous variables and Chi-square test for categorical variables. Analyses were carried out using MATLAB R2015a (The MathWorks, Inc., Natick, Massachusetts, United States) and R (R Core Team, 2012) software.

Results

In total 932 patients with COPD were eligible for analysis. Figure 1 shows the flow of participants through the study. Patients excluded due to irregular sleeping patterns and not enough time in bed had significantly lower FEV_1 % predicted compared with included patients (46·6±19·4 vs. 50·8±20·5, p<0·05). No significant differences between included and excluded patients were observed for age, gender, body mass index (BMI), smoking status and MMRC. The median number of days analyzed per patient was six (four weekdays + Saturday and Sunday), resulting in a total of 5646 valid assessed days, of which 3788 (67%) were weekdays. Demographic and clinical characteristics of the patients included in the study are presented in Table 2 (those of excluded patients can be found in Supplementary Materials Table 1, appendix p 16).

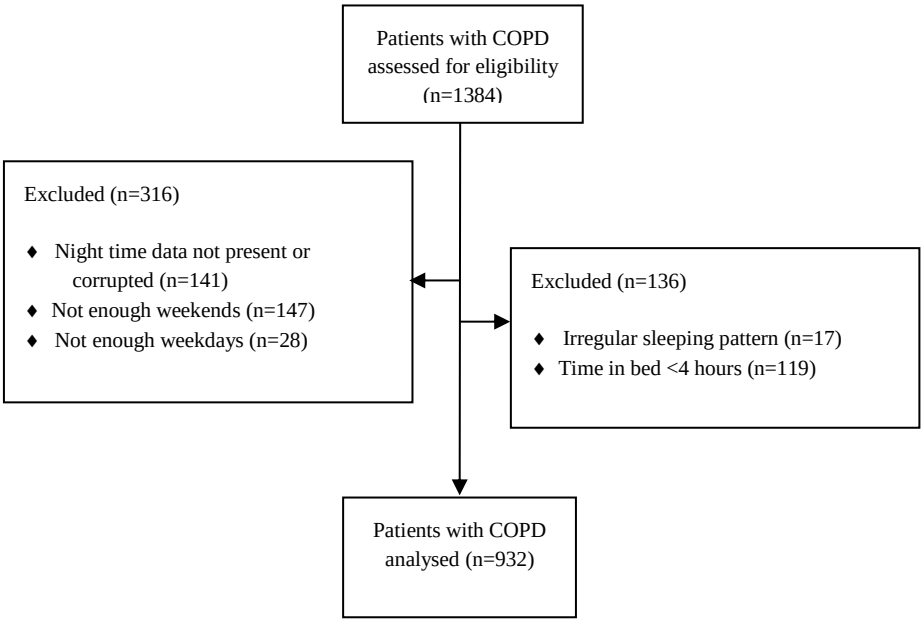

Figure 1 Flow of patients through the study

Table 2: Demographic and clinical characteristics.

	Included patients (n=932)
Male / female (%)	65·6 / 35·4
Smokers / non smokers (%)	32·6 / 67·4
Age (yr)	66·4±8·3
BMI (kg/m^2)	26·3±5·4
FEV_1 % predicted	50·8±20·5
GOLD 1 - 2 - 3 – 4 (%)	9·6 – 40·2 – 32·4 – 17·8
MMRC* 0 - 1 - 2 - 3 – 4 (%)	13·9 – 26·8 – 21·9 – 17·6 – 6·1

*Data in the table are expressed as percentages, or means ± standard deviation. BMI: Body Mass Index, FEV_1: forced expiratory volume in 1 s, GOLD: Global Initiative for Chronic Obstructive Lung Disease grade, MMRC: modified Medical Research Councils scale. *MMRC data for 805 patients.*

Sleep measures evaluation in patients with COPD

Figure 2 shows the associations of nighttime and daytime sleep measures with disease severity, dyspnea, gender, and day group. In particular, the total night sleeping time was significantly higher in women and during weekends (Fig. 2A). The number of nocturnal sleeping bouts (Fig. 2B) increased both with airflow limitation and exertional dyspnea. In particular, it was significantly higher in patients who had the most severe airflow limitation and who were the most dyspneic. The number of nocturnal sleeping bouts was significantly higher in men and during weekends. Both short duration of nocturnal sleeping bouts and low sleep efficiency were associated with a higher GOLD grade and dyspnea score (Fig. 2C-D). These two sleep measures were significantly higher for women. The time spent awake after the first sleep onset increased both with disease severity and dyspnea, being worst in patients with GOLD grade 4 and MMRC score 4 (Fig. 2E).

During daytime the sleeping time increased significantly with dyspnea (Fig. 2F), as did the number and duration of sleeping bouts (Fig. 2G-H). Sleeping time and duration of sleeping bouts were significantly shorter in patients with GOLD grade 4.

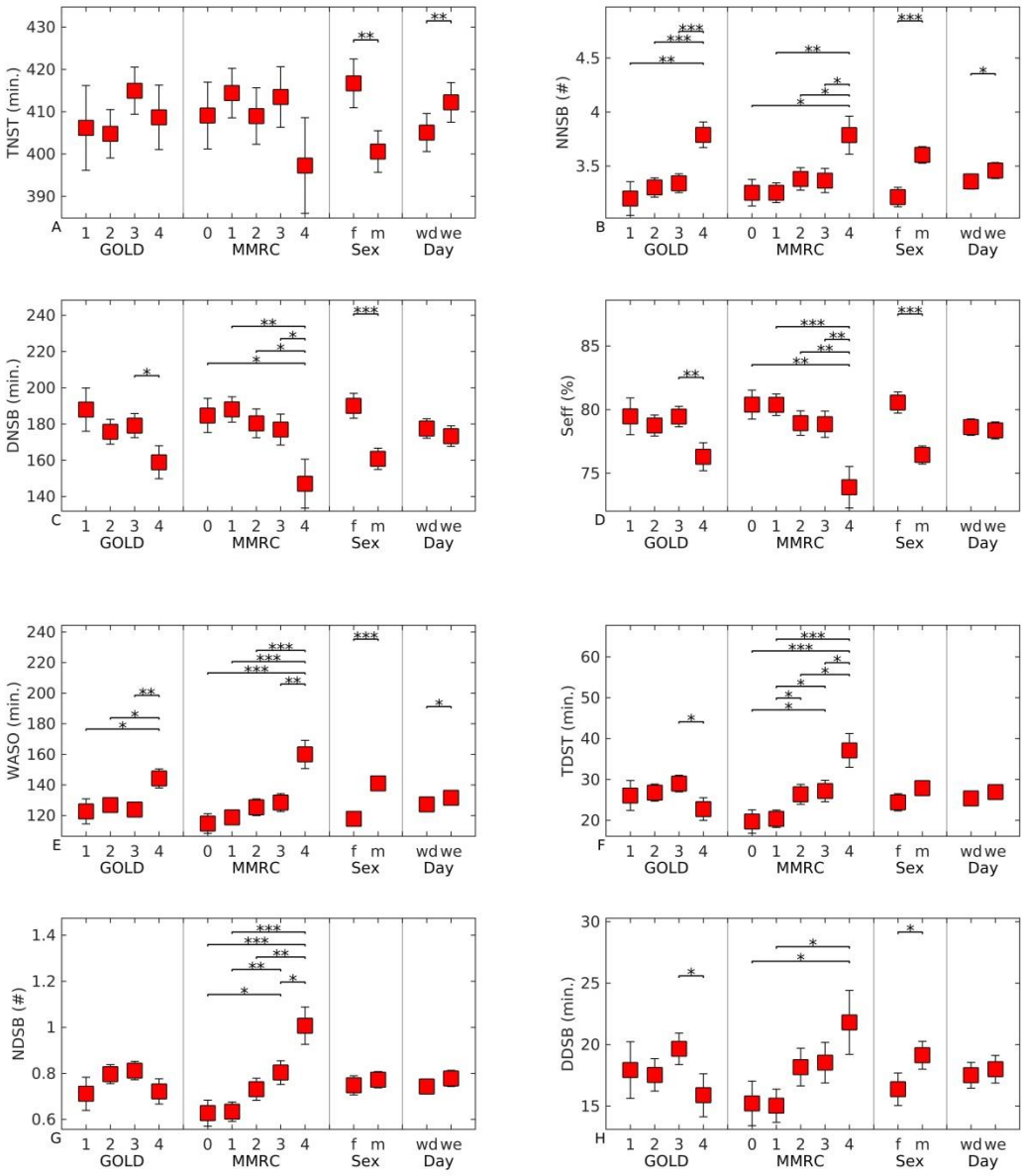

*Figure 2 Impact of disease severity according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades, daytime dyspnea according to the modified Medical Research Council (MMRC) scale, sex (f = female, m = male), and day group (wd = weekdays, we = weekends) on sleep parameters (A: TNST = Total Night Sleeping Time; B: NNSB = Number of Nocturnal Sleeping Bouts; C: DNSB = average Duration of Nocturnal Sleeping Bouts; D: Seff = Sleep efficiency; E: WASO = time aWake After the first Sleep Onset ; F: TDST = Total Day Sleeping Time; G: NDSB = Number of Daytime Sleeping Bouts; H: DDSB = average Duration of Daytime Sleeping Bouts). Data are expressed as least-square means ± standard error. Significance levels for pairwise comparisons are indicated as horizontal bars with *=p<0·05, **=p<0·01, and ***=p<0·001.*

Association between objective sleep measures and daytime physical activity

Nocturnal sleep measures were divided into quartiles (Q_1, shortest/lowest-Q_4, longest/highest) to assess the association with daytime physical activity measures (Supplementary Materials Table 2, appendix p 18).

As shown in Fig. 3A, the number of steps performed during the day decreased as the number of sleeping bouts and the minutes spent awake after the sleep onset increased. Patients who had their sleep characterized by long sleeping bouts and high sleep efficiency had a significantly higher number of steps on the following day. Patients who slept more than 480 minutes (Q_4) performed a smaller number of steps than the other patients, but no significant differences were found if the number of steps of each patient is divided by the time spent awake (data not shown). As presented in Fig. 3B, the time spent in very light activities was higher in patients who slept more and it increased with sleep fragmentation and time spent awake after the sleep onset. Patients with lower sleep efficiency and shorter sleeping bouts spent more time in very light activities. Patients with a higher number of sleeping bouts per night, shorter sleeping bouts, lower sleep efficiency and longer time spent awake during the night spent less time in light (Fig. 3C) and moderate-to-vigorous (Fig. 3D) physical activities. Patients who slept more during the night spent less time in light activities, while less time in moderate-to-vigorous was spent by those who slept less during the night.

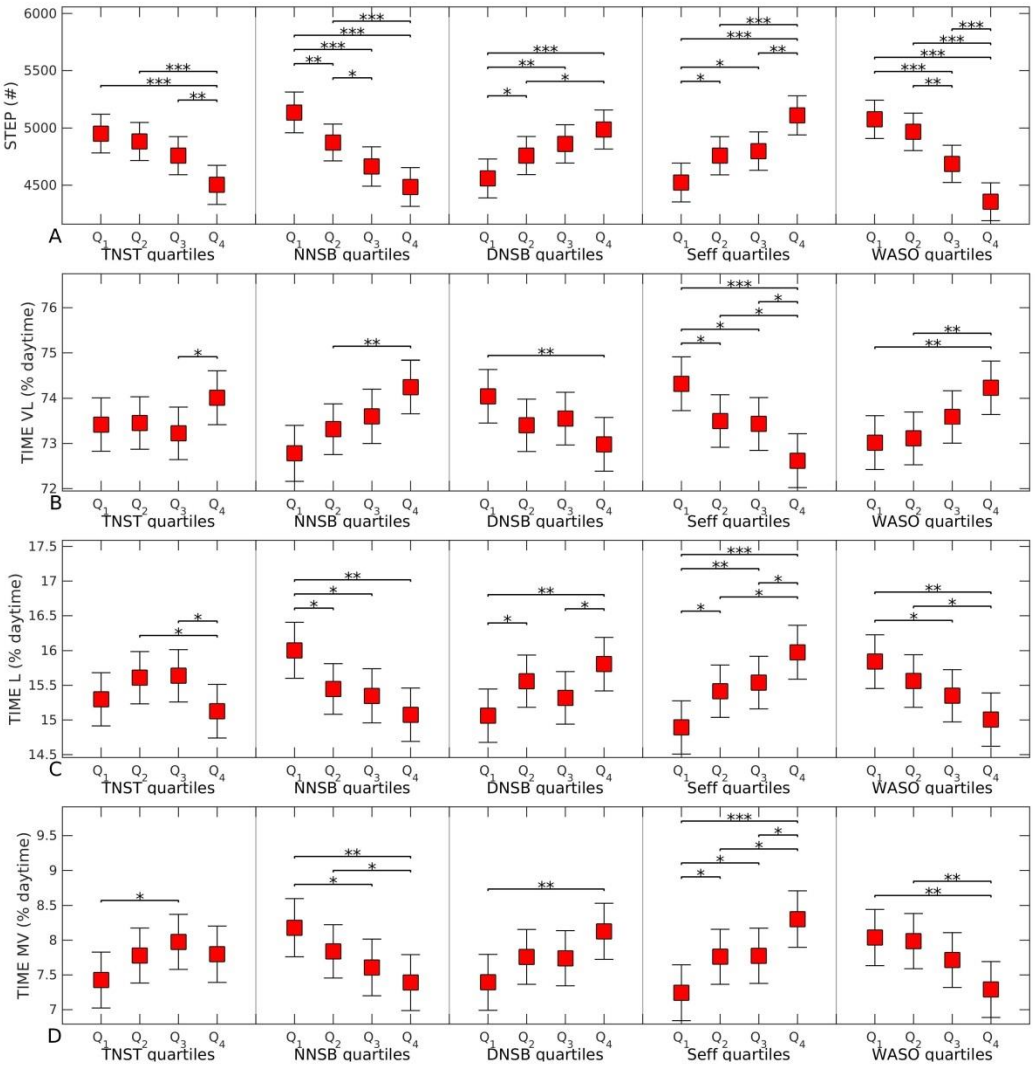

*Figure 3 Association between nocturnal sleep parameters (TNST = Total Night Sleeping Time; NNSB = Number of Nocturnal Sleeping Bouts; DNSB = average Duration of Nocturnal Sleeping Bouts; Seff = Sleep efficiency; WASO = time aWake After the first Sleep Onset) and daytime physical activity measures (A: STEP = Steps performed; B: TIME VL = Time spent in Very Light activity, C: TIME L = Time spent in Light activity, D: TIME MV = Time spent in Moderate-to-Vigorous activity). Data are expressed as least-square means ± standard error. Significance levels for pairwise comparisons are indicated as horizontal bars with *=p<0·05, **=p<0·01, and ***=p<0·001. TIME VL, TIME L, TIME VM are presented in % of the out of bed time.*

Daytime sleep was inversely related to the amount of nocturnal sleep, the duration of sleeping bouts and the sleep efficiency (Fig. 4). Patients who showed relatively short sleep duration during the night, who had short sleeping bouts and low sleep efficiency reported more daytime sleep.

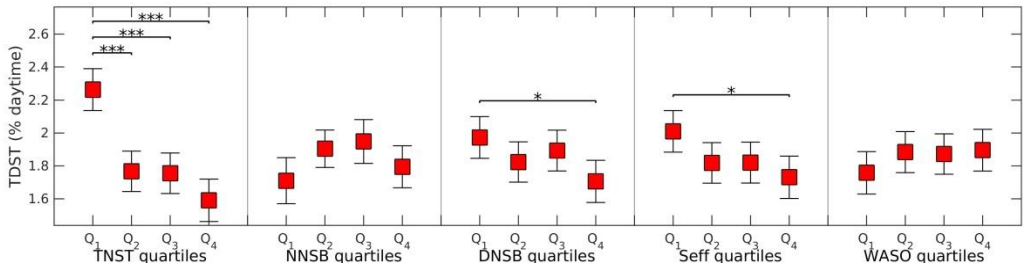

*Figure 4 Association between nocturnal sleep parameters (TNST = Total Night Sleeping Time; NNSB = Number of Nocturnal Sleeping Bouts; DNSB = average Duration of Nocturnal Sleeping Bouts; Seff = Sleep efficiency; WASO = time aWake After the first Sleep Onset) and Total Day Sleeping Time (TDST). Data are expressed as least-square means ± standard error. Significance levels for pairwise comparisons are indicated as horizontal bars with *=p<0·05, **=p<0·01, and ***=p<0·001. TDST is presented in % of the out of bed time.*

Discussion

We describe, to our knowledge, the first study in a large sample of participants with COPD, targeting the association of objectively measured sleep impairment with airflow limitation, exertional dyspnea, gender, day group and daytime activity levels.

We found that objective sleep quality measures are worse in patients with severe airway obstruction and dyspnea. This is in agreement with George et al.[17] who showed that subjective sleep disturbances tend to be more severe with advancing disease and with Dodge et al.[18] who showed that patients with dyspnea are more likely to report persistent sleep disturbance. Conversely, Hartman et al.[7] failed to find a significant association between night's rest parameters assessed by an accelerometer and both airflow limitation and dyspnea. However, this latter study did not evaluate sleep quality measures, but rather quantitative parameters such as body movements and number of posture transitions that are not necessarily related to poor sleep quality.[7] Nunes et al.[6] reported that the MMRC score was an important predictor of objectively measured sleep quality in 26 patients with moderate to very severe COPD. However, the small sample size precluded any firm conclusions on the differences between patients with different dyspnea scores. Furthermore, in this study patient's daily sleep logs were used. This may be problematic because sleep logs are imprecise in quantifying time in bed and wake time.[19]

The strong evidence provided by our findings regarding the association of sleep impairment with the most severe stage of the disease and dyspnea could be explained by at least two mechanisms. The lying sleeping position assumed by the participants in the study increases both work of breathing and airway resistance, and lowers their threshold for dyspnea.[20,21] Moreover, patients with severe COPD frequently experience episodes of worsening symptoms that may also preclude from adequate sleep. It has been shown that one night of sleep deprivation can lead to small but statistically significant falls in FEV_1 and forced vital capacity in a group of patients with COPD.[22] Although a single night's loss of sleep does not have major clinical consequences,

it may be speculated that chronic alterations in sleep would result in cumulative negative effects on the respiratory function, which could become relevant along the prolonged course of this disorder because they occur more likely for those patients who are least able to tolerate any further challenge to their ventilatory capability.

Participants with the most severe disease had worse sleep but they did not seem to compensate it during the day by adding naps. Most dyspneic patients, in turn, seemed to do so. Other investigators have also found that daytime sleepiness was related more strongly to the presence of respiratory symptoms than to a diagnosis of lung disease or the degree of airway obstruction.[23]

We saw significant gender differences after correction for age, BMI, smoking status, country of origin, GOLD and MMRC. Men had worse sleep quality measures and spent more time sleeping during the day than women. There is currently only limited information regarding the influence of gender on sleep in COPD. In a previous study using actigraphy no significant gender-related differences in sleep quality were found.[6] Other studies have documented that women appear to report more sleep-related complaints.[24] However, objective and subjective assessments of sleep seem to reflect different aspects and may therefore not be necessarily in agreement.[25]

During weekends patients had significant more fragmented sleep and spent significantly more time awake after the first sleep onset than during weekdays. Nonetheless, our results showed that impaired sleep during weekends may be compensated by sleeping longer.

This study showed that nights of lower sleep quality were followed by days of lower levels of physical activity in people with COPD. The robustness of the results was verified by controlling for several confounding factors such as severity of airflow limitation and severity of dyspnea. The association of impaired sleep with worse daytime performance is consistent with findings showing that it could play a substantial role in daytime symptoms and chronic fatigue.[26] Moreover these findings are consistent with other correlational evidence drawn from older adults suggesting that objectively measured poor sleep was associated with worse daytime physical function, yet none of these studies demonstrates a direct effect of sleep on subsequent physical activity.[8,9] Although inferring a causal relationship was out of the scope of this study, our finding provided a good illustration of the sequential association as it incorporated a clear chronological order of the predictor (sleep quality measure) and the predicted variable (physical activity). However, the possibility that poor daytime performance may be a causative factor for poor sleep quality should be considered.

The deficit in good sleep, in association with changes of sleep architecture, may make sleep not as restorative as needed and may cause a significant sleep deficit.[27] Accordingly, our study provides evidence to suggest that poor sleep efficiency and short sleeping bouts during the night are possibly compensated by additional daytime naps.

The fact that poor sleep quality was associated with reduced physical activity levels may have important consequences with regard to current clinical practice. First, our findings suggest the

possibility of increasing spontaneous engagement in physical activity through improving sleep since, in the absence of any intervention, patients having had a better night of sleep spontaneously engaged in more physical activity the following day. Second, existing strategies for promoting physical activity tend to focus on actions during the day. Additional efforts in promoting quality sleep among physically inactive subgroups may increase the overall impact of these interventions. Finally, sleep should be assessed and taken into account when analyzing physical activity in COPD, although recent literature is often-overlooking the continuity between nighttime sleep and daytime physical activity.[28]

This study has some limitations which should be considered when interpreting the results. Our participants were not screened for sleep-related disorders, such as obstructive sleep apnea (OSA). However, because COPD and OSA are both common chronic conditions, these should be expected to occur together, particularly among overweight individuals with COPD.[29] Moreover, it has been demonstrated that there are no differences in measures of dyspnea, sleep quality, sleep efficiency, and sleepiness during the day between patients with COPD only and patients with COPD-OSA overlap.[29] Although we cannot know whether the patients included had OSA, we can rule out that specific interventions influenced quality or quantity of sleep since only baseline data were analyzed. Nowadays, sleep assessment in COPD is mainly based on self-reported measures of sleep duration and quality, which have poor precision and reliability when compared to objective measures.[4,8,10] Activity monitors provide minimally invasive measures of the continuity and hence quality of sleep and they have the advantage of allowing recording continuously for 24-hours a day for extended periods.[10] However, to the current authors' knowledge, the SenseWear armband has not been properly validated to study sleep in COPD, even though its reliability has been shown in several sleep studies.[12,30]

In summary, sleep impairment in patients with COPD tends to be more pronounced in patients with severe airflow limitation and in those with worse exertional dyspnea. Moreover, nocturnal sleep impairment appears to be an important factor associated with the capability to engage in physical activity on a day-to-day basis. In particular, nights of better sleep quality measures were followed by days of higher levels of physical activity. Further research is needed to identify the causal association between nighttime sleep and the decline in daytime physical activity, as well as to assess whether the management of nighttime symptoms and the reduction of sleep impairment can improve physical activity in COPD patients. Considering both our current understanding of the negative health consequences of sleep disturbance in COPD and the current limited efficacy of interventions in significantly improving and maintain physical activity enhancement, our data suggest that approaches to improve sleep need to be considered as additional targets for tailored interventions and may have a favorable impact on lifestyle in patients with COPD.

Contributors

G. S., M.A.S., A.C.d.B., conceived and designed the analysis. G.S. analyzed the data and drafted the first version of the manuscript. M.A.S. and A.C.d.B. provided advice at all stages of the analysis. A.C.d.B. provided statistical support.
M.A.S., J.A., R.P.B., P.M.A.C., C.F.C., R.W.C., D.D-G., S.D., J.G-A., A.J.R.v.G., M.G., N.A.H., K.H., N.S.H., D.J., M.K., A.K., J.D.L., H.M., F.M., W.D-C.M., Z.J.McK., R.M., D.M., F.P., S.J.S., F.W.J.M.S., R.T-S., B.V., B.W., H.W., E.F.M.W., S.Z. contributed to the acquisition of data in each center included and/or participated in the critical revision of the manuscript. All authors accepted the final version of the manuscript.

Acknowledgment

The authors would like to thank Prof. R. Aarts, Dr. X. Long, Dr. J. W. Bikker, Prof. R. L. ZuWallack for the useful input provided to the manuscript. The Eindhoven-based authors and the CIRO-based authors gratefully acknowledge the financial support received by the iCare4COPD Project of Agentschap NL under Contract PNE101005. The Basel-based authors gratefully acknowledge the financial support received by the foundations ‘Gottfried und Julia Bangerter-Rhyner-Stiftung’, ‘Freiwillige Akademische Gesellschaft Basel’ and ‘Forschungsfonds der Universität Basel’.

References

1. Lozano, Rafael, et al. "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010." The Lancet 380.9859 (2013): 2095-2128.

2. Watz, Henrik, et al. "An official European Respiratory Society statement on physical activity in COPD." European Respiratory Journal 44.6 (2014): 1521-1537.

3. Gimeno-Santos, Elena, et al. "Determinants and outcomes of physical activity in patients with COPD: a systematic review." Thorax (2014): thoraxjnl-2013.

4. Agusti, A., et al. "Night-time symptoms: a forgotten dimension of COPD. "European Respiratory Review 20.121 (2011): 183-194.

5. Kinsman, R. A., et al. "Symptoms and experiences in chronic bronchitis and emphysema." CHEST Journal 83.5 (1983): 755-761.

6. Nunes, Deuzilane M., et al. "Actigraphic assessment of sleep in chronic obstructive pulmonary disease." Sleep and Breathing 17.1 (2013): 125-132.

7. Hartman, J. E., et al. "Frequent sputum production is associated with disturbed night's rest and impaired sleep quality in patients with COPD." Sleep and Breathing (2015): 1-9.

8. Goldman, Suzanne E., et al. "Poor sleep is associated with poorer physical performance and greater functional limitations in older women." Sleep 30.10 (2007): 1317.

9. Dam, Thuy-Tien L., et al. "Association between sleep and physical function in older men: the osteoporotic fractures in men sleep study." Journal of the American Geriatrics Society 56.9 (2008): 1665-1673.

10. Ancoli-Israel, S., et al. "The role of actigraphy in the study of sleep and circadian rhythms. American Academy of Sleep Medicine Review Paper." Sleep 26.3 (2003): 342-392.

11. Cormick, W. E. S. L. E. Y., et al. "Nocturnal hypoxaemia and quality of sleep in patients with chronic obstructive lung disease." Thorax 41.11 (1986): 846-854.

12. Sharif, Munir M., and Ahmed S. BaHammam. "Sleep estimation using BodyMedia's SenseWear™ armband in patients with obstructive sleep apnea." Annals of thoracic medicine 8.1 (2013): 53.

13. Watz, Henrik, et al. "Physical activity in patients with COPD." European Respiratory Journal 33.2 (2009): 262-272.

14. Troosters, Thierry, et al. "Physical inactivity in patients with COPD, a controlled multi-center pilot-study."Respiratory medicine 104.7 (2010): 1005-1011.

15. Garber, Carol Ewing, et al. "American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise." Medicine and science in sports and exercise 43.7 (2011): 1334-1359.

16. Goodnight, James Howard. "Tests of hypotheses in fixed effects linear models." Communications in Statistics-Theory and Methods 9.2 (1980): 167-180.

17. George, Charles FP, and Charles D. Bayliff. "Management of insomnia in patients with chronic obstructive pulmonary disease." Drugs 63.4 (2003): 379-387.

18. Dodge, Russell, Martha G. Cline, and Stuart F. Quan. "The natural history of insomnia and its relationship to respiratory symptoms." Archives of internal medicine 155.16 (1995): 1797-1800.

19. Morselli, Lisa, et al. "Role of sleep duration in the regulation of glucose metabolism and appetite." Best Practice & Research Clinical Endocrinology & Metabolism 24.5 (2010): 687-702.

20. Martin R. Nocturnal asthma: an overview. In: Martin R, ed. Nocturnal asthma. Mechanisms and treatment. Mount Kisco, NY: Futura Publishing; 1993:71-115.

21. Eltayara L, Ghezzo H, Milic-Emili J. Orthopnea and tidal expiratory flow limitation in patients with stable COPD. Chest 2001;119:99-104.

22. Phillips, Barbara A., K. R. Cooper, and T. V. Burke. "The effect of sleep loss on breathing in chronic obstructive pulmonary disease." CHEST Journal 91.1 (1987): 29-32.

23. Klink, M. E., R. Dodge, and S. F. Quan. "The relation of sleep complaints to respiratory symptoms in a general population." Chest Journal 105.1 (1994): 151-154.

24. Collop NA, Adkins D, Phillips BA. “Gender differences in sleep and sleep-disordered breathing.” Clin Chest Med. 2004 Jun;25(2):257-68.

25. Vgontzas, Alexandros N., et al. "Validity and clinical utility of sleep laboratory criteria for insomnia." International journal of neuroscience 77.1-2 (1994): 11-21.

26. Breslin, Eileen, et al. "Perception of fatigue and quality of life in patients with COPD." CHEST Journal 114.4 (1998): 958-964.

27. Wesensten, Nancy Jo, Thomas J. Balkin, and Gregory Belenky. "Does sleep fragmentation impact recuperation? A review and reanalysis." Journal of Sleep Research 8.4 (1999): 237-245.

28. Demeyer, Heleen, et al. "Standardizing the analysis of physical activity in patients with COPD following a pulmonary rehabilitation program." CHEST Journal 146.2 (2014): 318-327.

29. Soler, Xavier, et al. "High prevalence of obstructive sleep apnea in patients with moderate to severe COPD." Annals of the American Thoracic Society ja (2015).

30. Al Otair, Hadil, et al. "Assessment of sleep patterns, energy expenditure and circadian rhythms of skin temperature in patients with acute coronary syndrome." Medical Science Monitor: International Medical Journal of Experimental and Clinical Research 17.7 (2011): CR397.

Supporting Information

File Supplementary appendix.

(DOC)