Impact of comorbidities on physical activity in COPD

NORIANE A. SIEVI, OLIVER SENN, THOMAS BRACK, MARTIN H. BRUTSCHE, MARTIN FREY, SAROSH IRANI, JÖRG D. LEUPPI, ROBERT THURNHEER, DANIEL FRANZEN, MALCOLM KOHLER, AND CHRISTIAN F. CLARENbach

Pulmonary Division, University Hospital of Zurich, Institut of General Practice and Health Services Research and Zurich Centre for Integrative Human Physiology, University of Zurich, Zurich, Pulmonary Division, Cantonal Hospital of Glarus, Glarus, Pulmonary Division, Cantonal Hospital of St Gallen, St Gallen, Pulmonary Division, Clinic Barmelweid, Barmelweid, Pulmonary Division, Cantonal Hospital of Aarau, Aarau, University Clinic of Internal Medicine, Cantonal Hospital Basel and University of Basel, Basel and Pulmonary Division, Cantonal Hospital of Münsterlingen, Münsterlingen, Switzerland

ABSTRACT
Background and objective: Both comorbidities and physical inactivity have been shown to impair quality of life and contribute to hospital admissions and mortality in chronic obstructive pulmonary disease (COPD) patients. We hypothesized that the comorbid status predicts the level of daily physical activity (PA) in COPD.

Methods: In 228 patients with COPD (76% men; median (quartiles) age: 64 (59/69) years; percentage of predicted forced expiratory volume in 1 s (FEV1 % pred): 44 (31/63)), comorbidities were assessed by medical history, clinical interviews, examination and blood analysis. PA level (PAL) was measured by an activity monitor (SenseWear Pro, Bodymedia Inc., Pittsburgh, PA, USA). The association between PAL and comorbidities was investigated by univariate and multivariate regression analysis.

Results: Seventy-nine per cent of the COPD patients had at least one additional chronic comorbidity, 56% had two or more comorbidities and 35% had three or more comorbidities. In univariate analysis body mass index, the number of pack years and having at least one additional comorbidity was negatively associated with PAL while there was a positive nonlinear association between FEV1 and PAL. The presence of at least one additional comorbidity was negatively associated with PAL while there was a positive nonlinear association between FEV1 and PAL. The presence of at least one additional comorbidity was negatively associated with PAL irrespective of airflow limitation.

Conclusions: In this cohort, almost 80% of COPD patients had at least one additional chronic comorbidity. The level of daily PA seems to be significantly impaired by the presence of comorbidities irrespective of the type of comorbidity and independent of the degree of airflow limitation.

SUMMARY AT A GLANCE
This study investigated the impact of comorbidities on the level of daily PA in COPD patients. The level of daily PA seems to be significantly impaired by the presence of comorbidities irrespective of the type of comorbidity and independent of the degree of airflow limitation.

INTRODUCTION
Comorbidities are common in patients with chronic obstructive pulmonary disease (COPD). Van Manen et al. reported that almost 23% of COPD patients had three or more comorbidities. However, knowledge on the prevalence and type of comorbidities in patients with COPD is still limited and varies considerably between studies. Previous studies demonstrated that comorbidities impair quality of life, and contribute to hospitalizations and mortality in COPD patients.

Data from the Towards a Revolution in COPD Health study showed that COPD patients die more frequently from a comorbid condition than from COPD itself. It is a matter of current research if comorbidities simply co-occur in a typically elderly population of COPD patients or if they are at least partly a consequence of COPD depending on severity of airflow limitation. In
this context, it could be hypothesized that the evolution of comorbidities is a consequence of an underlying shared condition that typically occurs in COPD such as physical inactivity. Physical activity (PA) is known to be a strong predictor for all-cause mortality in patients with COPD.\textsuperscript{8} Watz et al.\textsuperscript{9} reported that COPD patients showed reduced PA compared with healthy subjects. In a questionnaire-based study by Garcia-Aymerich et al.\textsuperscript{10} that included 364 severe COPD patients, the impact of having at least one additional chronic comorbidity on PA was evaluated. There was no significant difference in having at least one additional chronic comorbidity among low, moderately and highly active COPD patients. However, to date, the impact of comorbidities on objectively measured PA in patients with COPD has not been evaluated.

Therefore, the aim of our study was to evaluate the impact of the comorbid status on objectively measured PA in patients with COPD.

**METHODS**

**Subjects**

This study was performed as part of The Obstructive Pulmonary Disease Outcomes Cohort of Switzerland (TOPDOCS) (http://www.topdocs.ch). TOPDOCS is an ongoing prospective, non-interventional cohort study including COPD patients from seven study centres in Switzerland. Patients were recruited during ambulatory visits in the pulmonary clinics or during hospital stay. Patients aged between 40 and 75 years with objectively confirmed COPD according to The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines\textsuperscript{11} were assessed for eligibility between October 2010 and August 2013. Patients were excluded if they had suffered from a COPD exacerbation within the last 6 weeks or if they suffered from mental or physical disability precluding informed consent or compliance with the protocol. The study was conducted in accordance with the declaration of Helsinki of the World Medical Association. The Ethics Committee of the Canton of Zurich approved the study (EK-ZH-NR: 2011-0106), and the study was registered at http://www.ClinicalTrials.gov, NCT01527773. All subjects gave written informed consent to participate.

**Measurements**

**Comorbidities**

Comorbidities were assessed by examination of the documented medical history, clinical interviews, clinical examination and blood analysis. The International Classification of Diseases—Tenth Revision\textsuperscript{12} was used for classifying the comorbidities. Obesity was defined according to the World Health Organization definition (body mass index (BMI) ≥ 30 kg/m\textsuperscript{2}). In the analysis, only diseases with a prevalence of >5% were considered.

**Physical activity**

Patient’s data were recorded over 7 consecutive days by a multisensory band (SenseWear Pro, Bodymedia Inc., Pittsburgh, PA, USA) that was worn on the upper left arm over the triceps muscle. The threshold for valid data from the armband was set at 4 days with a minimum of 22.5 h/day. PA level (PAL) was assessed. PAL is an objective measure of daily PA and is defined as the total daily energy expenditure divided by energy expenditure during sleep.\textsuperscript{9} A PAL of ≥1.70 defines an active person, a PAL between 1.40 and 1.69 a sedentary person and <1.40 defines a very inactive person.\textsuperscript{9,13} Additionally, the number of steps per day and the time spent in at least moderate PA (three metabolic equivalent of task (MET)) were recorded.

**Lung function**

All participants underwent standard pulmonary functional testing according to American Thoracic Society guidelines\textsuperscript{14} to measure forced expiratory volume in 1 s (FEV\textsubscript{1}) and forced vital capacity. Only values after bronchodilatation are reported.

**Statistical analysis**

All results are shown as median and quartiles unless otherwise stated. Statistical analysis was performed with Statistica V6.0 (StatSoft, Tulsa, OK, USA) and STATA 12 (StataCorp, College Station, TX, USA).

In each COPD patient, the number of comorbidities was assessed and categories from 0 to ≥5 were formed. Univariate regression analysis was used to investigate associations between PAL (dependent variable) and comorbidity categories as well as possible predictors for PA such as age, gender, BMI, pack years of smoking and FEV\textsubscript{1}% predicted (pred). To further investigate the independent association between PAL and comorbidities, multivariate analysis involved regression of variables that showed a univariate regression P-value of <0.1 with adjustment for FEV\textsubscript{1}% pred. as potential confounder. Analysis of covariance was performed to estimate the adjusted mean PAL levels (standard errors (SE)) for the comorbidity categories.

To take into account a non-linear association between PAL and FEV\textsubscript{1}% pred., the squared term of FEV\textsubscript{1}% pred. (FEV\textsubscript{1}% pred. × FEV\textsubscript{1}% pred.) was included in the analysis. The final model was used applying transformed PAL values and residual analysis of the model was performed to verify the regression assumptions.

In addition, PAL as dependent variable was replaced by the number of steps per day and the time spent in at least moderate activity (≥3 MET) in the final regression model to verify a possible association between different measures of PA and comorbid status.

A two-sided P-value of <0.05 was considered to be statistically significant.

**RESULTS**

**Study participants**

Two hundred twenty-eight COPD patients (42% GOLD stage I/II, 36% III, 22% IV) entered the final analysis (Fig. 1). The median (quartiles) age was 64...
(58.5/68.5) years, BMI was 25.7 (22.3/28.4) kg/m² and 25% of the COPD patients were current smokers. Median PAL (quartiles) of all COPD patients was 1.43 (1.30/1.61), in COPD patients without comorbidities 1.58 (1.40/1.75) and in COPD patients with one or more additional comorbidities 1.40 (1.28/1.57). The detailed patient characteristics are shown in Table 1.

Prevalence of comorbidities
Seventy-nine per cent of the COPD patients had at least one additional comorbidity, 56% had two or more comorbidities and 35% had three or more comorbidities. The prevalence of the different comorbidities in the cohort of COPD patients is shown in Figure 2. The most prevalent comorbidities included arterial hypertension (48%), coronary artery disease (19%) and obesity (22%).

Predictors of PAL
In univariate regression analysis, PAL was negatively associated with BMI, pack years of smoking and with having at least one additional comorbidity, respectively. Non-linear FEV₁ % pred. was positively associated with PAL (Table 2). Table 3 shows the independent determinants of PAL based on the multiple regression analysis. PAL was negatively associated with the occurrence of at least one additional comorbidity. Furthermore, a non-linear positive association between PAL and FEV₁ % pred. has been observed. Mean (SE) adjusted PAL levels according to the number of comorbidities are displayed in Figure 3. COPD patients with one or more additional comorbidity showed a significantly decreased PAL compared with patients without comorbid conditions. There was no significant difference between the adjusted PAL in those with only one compared with

### Table 1 Patient characteristics

| Characteristic          | n = 228 |
|-------------------------|---------|
| Age, years              | 64 (58.5/68.5) |
| Gender (M/F)            | 151/77  |
| BMI, kg/m²              | 25.7 (22.3/28.4) |
| Current smoker, n (%)   | 57 (25) |
| Pack years of smoking, n| 40 (26.0/60.0) |
| FEV₁, % pred.           | 44 (31.0/63.0) |
| FVC, % pred.            | 81 (64.5/93.0) |
| RV/TLC, %               | 56 (11.7) |
| TLco, % pred.           | 45 (35/67) |
| Number of comorbidities, n | 2 (1/3) |
| SenseWear wearing time, days | 5.9 (4.9/6.0) |
| Physical activity level  | 1.43 (1.30/1.61) |
| Number of steps per day, n | 4140 (2364/6609) |
| Time spent in at least 3 MET, min | 54 (23/115) |

Values are median (quartiles). BMI, body mass index; FEV₁, forced expiration in 1 s; FVC, forced volume capacity; MET, metabolic equivalent of task; RV, residual volume; TLC, total lung capacity; TLco, diffusing capacity for carbon monoxide.
Table 2  Univariate regression analysis of possible predictors for PAL

|                        | B            | 95% confidence interval | P-value |
|------------------------|--------------|-------------------------|---------|
| Age, years             | -0.00        | -0.01/-0.00             | 0.172   |
| Gender (M/F)           | -0.10        | -0.12/-0.01             | 0.076   |
| BMI, kg/m²             | -0.01        | -0.01/-0.00             | 0.003*  |
| Pack years of smoking, n| -0.00        | -0.00/-0.00             | 0.006*  |
| Linear FEV₁% pred.    | 0.00         | -0.00/0.00              | 0.151   |
| FEV₁% pred.           | 0.01         | -0.00/0.02              | 0.004*  |
| FEV₁% pred. x FEV₁% pred. (squared term) | -0.00 | -0.00/-0.00 | 0.008* |
| RV/TLC, %              | -0.00        | -0.01/-0.00             | 0.039*  |
| TLco, % pred.         | 0.00         | 0.00/0.00               | <0.001* |
| Comorbidities, category|             |                         |         |
| 0 comorbidities (reference) | 1.00 | -0.01/0.00 | 0.245  |
| 1 comorbidity          | -0.50        | -0.24/-0.76             | 0.001*  |
| 2 comorbidities        | -0.14        | -0.23/-0.05             | 0.002*  |
| 3 comorbidities        | -0.20        | -0.30/-0.10             | <0.001* |
| 4 comorbidities        | -0.17        | -0.28/-0.06             | 0.002*  |
| ≥5 comorbidities       | -0.29        | -0.40/-0.18             | <0.001* |

* P-value < 0.05.
BMI, body mass index; FEV₁, forced expiration in 1 s; PAL, physical activity level; RV, residual volume; TLC, total lung capacity; TLco, diffusing capacity for carbon monoxide.

Table 3  Multiple regression analysis of possible predictors for PAL

|                        | B            | 95% confidence interval | P-value |
|------------------------|--------------|-------------------------|---------|
| Age, years             | -0.00        | -0.01/-0.00             | 0.172   |
| Gender (M/F)           | -0.03        | -0.09/-0.23             | 0.287   |
| BMI, kg/m²             | -0.01        | -0.01/-0.00             | 0.108   |
| Pack years of smoking, n| -0.00        | -0.00/0.00              | 0.245   |
| Non-linear FEV₁% pred. | 0.01         | -0.01/0.26              | <0.001* |
| FEV₁% pred. x FEV₁% pred. (squared term) | -0.00 | -0.00/-0.00 | 0.001* |
| Comorbidities, category|             |                         |         |
| 0 comorbidities (reference) | 1.00 | -0.01/0.00 | 0.245  |
| 1 comorbidity          | -0.15        | -0.23/-0.06             | 0.001*  |
| 2 comorbidities        | -0.11        | -0.21/-0.03             | 0.010*  |
| 3 comorbidities        | -0.17        | -0.28/-0.07             | 0.001*  |
| 4 comorbidities        | -0.12        | -0.23/-0.01             | 0.031*  |
| ≥5 comorbidities       | -0.24        | -0.36/-0.13             | <0.001* |

* P-value < 0.05.
BMI, body mass index; FEV₁, forced expiration in 1 s; PAL, physical activity level.

DISCUSSION

This study investigated the prevalence of comorbidities and the impact of comorbidities on PAL in a heterogeneous group of COPD patients. The main findings of this study are that approximately 80% of COPD patients had at least one additional comorbidity, which was primarily a cardiovascular disease. The level of daily PA seems to be significantly impaired by the presence of comorbidities irrespective of the number and type of comorbidities and independent of the degree of airflow limitation.

Comorbidities are common in patients with COPD and influence the treatment and prognosis of COPD patients. The prevalence of having at least one comorbidity of almost 80% in our cross-sectional analysis may even be underestimated because of the fact that we decided a priori to include only comorbidities with a prevalence >5%. Comorbidities are associated with an increased risk of death in COPD patients. Previous studies investigated the prevalence of comorbidities in COPD patients. However, the prevalence rates for specific diseases vary considerably. A review by Chatila et al. suggested that the prevalence of arterial hypertension in

© 2015 Asian Pacific Society of Respirology
Comorbidities and daily activity in COPD

COPD patients vary from 18% to 52% between different studies, and the prevalence of cardiac disease in COPD ranges from 13% to 65%. Most of the studies investigating the prevalence of comorbidities in patients with COPD demonstrate that cardiovascular diseases represent the most frequent comorbid conditions in COPD. Similarly in our study, almost half of the patients had arterial hypertension, the most frequent comorbidity in our cohort, followed by coronary artery disease which was present in 20%. This high prevalence of cardiac comorbidities in COPD patients is in line with the observed increased risk for cardiovascular mortality in patients with COPD. A comparable prevalence of comorbidities was also found in a general practitioner based Swiss COPD cohort.

Physical inactivity is frequently observed in patients with COPD and has been shown to predict poor outcome, including more frequent hospital admissions compared with COPD patients who are physically active. Lower levels of PA are also known to be a strong predictor for all-cause mortality in patients with COPD. A recent longitudinal study demonstrated that COPD patients with a decline over time to a low PAL (questionnaire-based) had a higher all-cause mortality risk than patients who remained at the same or increased their level of regular PA compared with the baseline evaluation. To date, there are some studies investigating possible factors which may be associated with a reduction of PA in patients with COPD such as airflow obstruction and inflammation. In a recently published study by Van Remoortel et al., several risk factors including physical inactivity and comorbidities were evaluated in 60 persons with preclinical COPD. Physical inactivity as defined by a PAL < 1.4 was an independent risk factor of having ≥2 comorbidities. In contrast, the present study did not investigate in preclinical COPD but examined patients with moderate-to-severe COPD.

In the current COPD cohort, the main effect on PAL seems to depend on whether or not an individual patient has comorbidities. However, the effect on PAL seems not to depend on the actual number of comorbidities, as there was no significant difference between the adjusted PAL in those with only one compared with those with multiple comorbidities.

Several studies assessed the association between different measures of daily PA and FEV1 and showed that increased airflow obstruction is associated with a decreased daily PA. Of these studies, only the study by Watz et al. assessed objectively PAL as a measure of PA; GOLD stage III and IV were independently associated with PAL. In our study, there was also a non-linear independent association between objectively measured PAL and FEV1. These findings are comparable with the results of Watz and colleagues, suggesting a stronger association between PAL and FEV1% pred. in patients with severe COPD than in patients with mild/moderate COPD.

Garcia-Aymerich et al. studied the impact of chronic comorbidities on PA in patients with severe COPD. In this questionnaire-based study, there was no significant difference in having at least one additional comorbidity among low, moderately and highly active COPD patients. However, a subgroup of COPD patients with diabetes showed a negative association with PA. In contrast, our study showed that at least one additional comorbidity is independently associated with PAL in COPD patients. This conflicting finding may be due to the different measurements for assessing comorbidities and PA because self-reported PA questionnaires insufficiently reflect the actual level of daily PA. One could hypothesize that comorbidities may also be a consequence of physical inactivity in COPD. Both comorbidities and a reduced PAL have been shown to increase the risk of mortality in COPD. Thus, it is still a matter of debate whether the combined occurrence of comorbidities and reduced PAL leads to a higher risk of mortality.

The current study has some limitations. The cross-sectional study design does not allow a causal relationship between comorbidities and PAL in patients with COPD to be assessed. Further, only diagnosed comorbidities with a prevalence >5% were included in the analysis. Comorbidities with a prevalence <5% and possible additional undiagnosed comorbidities were not considered in the presented analysis, which may underestimate the currently presented prevalence of comorbidities. Because the impact of the different comorbidities on PAL is unknown in patients with COPD, we could not weigh their individual influence on PAL in the analysis. This should possibly be addressed in further studies on this topic. However, the main effect on PAL seems to depend on whether or not an individual patient has a comorbid condition.

In conclusion, our findings suggest that almost 80% of COPD patients have at least one additional comorbidity. The level of daily PA seems to be significantly impaired by the presence of comorbidities irrespective of the type of comorbidity and independent of the degree of airflow limitation.

Acknowledgements
This study was supported by Lunge Zurich, Lung League of both Basel, Gottfried and Julia Bangerter-Rhyner Foundation, Freiwillige Akademische Gesellschaft Basel, Lung League of Canton Thurgau, Lung League of Canton St Gallen, Lung league of Canton Aargau and Lung League of Canton Glarus.

REFERENCES
1. Vanfleteren LE, Spruit MA, Groenen M, Gaffron S, van Empel VP, Bruijnizeel PL, Rutten EP, Op ’t Roodt J, Wouters EF, Franssen FM. Clusters of comorbidities based on validated objective
measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 2013; **187**: 728–35.

2. Divo M, Cote C, de Torres JP, Casanova C, Marin JM, Pinto-Plata V, Zulueta J, Cabrera C, Zagaceta J, Hunninghake G *et al.* Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 2012; **186**: 155–61.

3. van Manen JG, Bindels PJ, Ilzermans CJ, van der Zee JS, Bottema BJ, Schade E. Prevalence of comorbidity in patients with a chronic airway obstruction and controls over the age of 40. *J. Clin. Epidemiol.* 2001; **54**: 287–93.

4. Chatila WM, Thomashow BM, Minai OA, Criner GJ, Make BJ. Comorbidities in chronic obstructive pulmonary disease. *Proc. Am. Thorac. Soc.* 2008; 5: 549–55.

5. Mannino DM, Thorn D, Swensen A, Holguin F. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *Eur. Respir. J.* 2008; **32**: 962–9.

6. Ferrer M, Alonso J, Morera J, Marrades RM, Khalaf A, Aguar MC, Plaza V, Prieto L, Anto JM. Chronic obstructive pulmonary disease stage and health-related quality of life. *The Quality of Life of Chronic Obstructive Pulmonary Disease Study Group. Ann. Intern. Med.* 1997; **127**: 1072–9.

7. McGarvey LP, John M, Anderson JA, Zvarich M, Wise RA. Ascertainment of cause-specific mortality in COPD: operations of the TORCH Clinical Endpoint Committee. *Thorax* 2007; **62**: 411–15.

8. Waschki B, Kirsten A, Holz O, Muller KC, Meyer T, Watz H, Magnussen H. Physical activity is the strongest predictor of all-cause mortality in patients with COPD: a prospective cohort study. *Chest* 2011; **140**: 331–42.

9. Watz H, Waschki B, Meyer T, Magnussen H. Physical activity in patients with COPD. *Eur. Respir. J.* 2009; **33**: 62–72.

10. Garcia-Aymerich J, Felez MA, Escarrabill J, Marrades RM, Morera J, Elosua R, Anto JM. Physical activity and its determinants in severe chronic obstructive pulmonary disease. *Med. Sci. Sports Exerc.* 2004; **36**: 1667–73.

11. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, Fukuchi Y, Jenkins C, Rodriguez-Roisin R, van Weel C *et al.* Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease—GOLD executive summary. *Am. J. Respir. Crit. Care Med.* 2007; **176**: 532–55.

12. World Health Organization. International Classification of Diseases (ICD), 2013. [Accessed 21 Sep 2013.] Available from URL: http://www.who.int/classifications/icd/en/

13. Manini TM, Everhart JE, Patel KV, Schoeller DA, Colbert LH, Visser M, Tylavsky F, Bauer DC, Goodpaster BH, Harris TB. Daily activity energy expenditure and mortality among older adults. *JAMA* 2006; **296**: 171–9.

14. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P *et al.* Standardisation of spirometry. *Eur. Respir. J.* 2005; **26**: 319–38.

15. Anthonisen NR, Connnett JE, Enright PL, Manfreda J. Hospitalizations and mortality in the Lung Health Study. *Am. J. Respir. Crit. Care Med.* 2002; **166**: 333–9.

16. Jochmann A, Neubauer F, Miedinger D, Scharfoth S, Tamm M, Leuppi JD. General practitioner’s adherence to the COPD GOLD guidelines: baseline data of the Swiss COPD Cohort Study. *Swiss Med. Wkly* 2010; **140**: w13053.

17. Garcia-Aymerich J, Lange P, Benet M, Schnohr P, Anto JM. Regular physical activity reduces hospital admission and mortality in chronic obstructive pulmonary disease: a population based cohort study. *Thorax* 2006; **61**: 772–8.

18. Vaes AW, Garcia-Aymerich J, Marott JL, Benet M, Groenen MT, Schnohr P, Franssen FM, Vestbo J, Wouters EF, Lange P *et al.* Changes in physical activity and all-cause mortality in COPD. *Eur. Respir. J.* 2014; **44**: 1199–209.

19. Bossenbroek L, de Greef MH, Wempe JB, Krijnen WP, Ten Hacken NH. Daily physical activity in patients with chronic obstructive pulmonary disease: a systematic review. *COPD* 2011; **8**: 306–19.

20. Watz H, Waschki B, Kirsten A, Muller KC, Kretschmar G, Meyer T, Holz O, Magnussen H. The metabolic syndrome in patients with chronic bronchitis and COPD: frequency and associated consequences for systemic inflammation and physical inactivity. *Chest* 2009; **136**: 1039–46.

21. Pitta F, Troosters T, Spruit MA, Probst VS, Decramer M, Gosselink R. Characteristics of physical activities in daily life in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 2005; **171**: 972–7.

22. Schonhofer B, Ardes P, Geibel M, Kohler D, Jones PW. Evaluation of a movement detector to measure daily activity in patients with chronic lung disease. *Eur. Respir. J.* 1997; **10**: 2814–19.

23. Belza B, Steele BG, Hunziker J, Lakshminaryan S, Holt L, Buchner DM. Correlates of physical activity in chronic obstructive pulmonary disease. *Nurs. Res.* 2001; **50**: 195–202.

24. Watz H, Waschki B, Boehme C, Clausen M, Meyer T, Magnussen H. Extrapulmonary effects of chronic obstructive pulmonary disease on physical activity: a cross-sectional study. *Am. J. Respir. Crit. Care Med.* 2008; **177**: 743–51.

25. Van Remoortel H, Hornikx M, Langer D, Burtin C, Everaerts S, Verhamme P, Boonen S, Gosselink R, Decramer M, Troosters T *et al.* Risk factors and comorbidities in the preclinical stages of chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 2014; **189**: 30–8.

26. van Gestel AJ, Clarenbach CF, Stowhas AC, Rossi VA, Sievi NA, Camden G, Russi EW, Kohler M. Predicting daily physical activity in patients with chronic obstructive pulmonary disease. *PLoS ONE* 2012; **7**: e48081.

27. Clarenbach CF, Senn O, Sievi NA, Camden G, van Gestel AJ, Rossi VA, Pulhan MA, Thornheer R, Russi EW, Kohler M. Determinants of endothelial function in patients with COPD. *Eur. Respir. J.* 2013; **42**: 1194–204.