Daily physical activity in subjects with newly diagnosed COPD

Rationale Information about daily physical activity levels (PAL) in subjects with undiagnosed chronic obstructive pulmonary disease (COPD) is scarce. This study aims to assess PA and to investigate the associations between PA and clinical characteristics in subjects with newly diagnosed COPD.

Methods Fifty-nine subjects with a new spirometry-based diagnosis of mild (n=38) and moderate (n=21) COPD (63±6 years, 68% male) were matched with 65 smoking controls (62±7 years, 75% male). PA (daily steps, time spent in moderate-to-vigorous intense physical activities (MVPA) and PAL) was measured by accelerometry. Dyspnoea, complete pulmonary function tests, peripheral muscle strength and exercise capacity served as clinical characteristics.

Results PA was significantly lower in COPD versus smoking controls (7986±2648 vs 9765 ±3078 steps, 64 (27–120) vs 110 (55–164) min of MVPA, 1.49±0.21 vs 1.62±0.24 PAL respectively, all p<0.05). Subjects with COPD with either mild symptoms of dyspnoea (mMRC 1), those with lower diffusion capacity (T_L,co), low 6 min walking distance (6MWD) or low maximal oxygen uptake (VO_2 peak) had significantly lower PA. Multiple regression analysis identified 6 MWD and T_L,co as independent predictors of PA in COPD.

Conclusions The reduction in PA starts early in the disease, even when subjects are not yet diagnosed with COPD. Inactivity is more pronounced in subjects with mild symptoms of dyspnoea, lower levels of diffusion capacity and exercise capacity.

The detection of an inactive lifestyle in patients with chronic obstructive pulmonary disease (COPD) is increasingly important since inactivity predicts prognosis in COPD[1] and may even impact on the rate of lung function decline.[2] Data on daily physical activity levels (PAL) are lacking regarding patients unaware of their disease in whom the diagnosis of COPD is based on spirometry screening (preclinical stage). We aimed to objectively investigate daily PALs and to investigate the association between physical activity and different clinical characteristics in subjects with newly spirometry-based diagnosis of COPD.

Hundred and twenty-four (ex-) smokers were recruited from a population-based sample (see online supplementary figure S1). Fifty-nine subjects with a new spirometry-based diagnosis of mild (n=38) and moderate (n=21) COPD (63±6 years, 68% male) were matched with 65 smoking controls (62 ±7 years, 75% male). Detailed characteristics of the study subjects are summarised in online supplementary table S1. Physical activity (daily steps, time spent in moderate-to- vigorous intense physical activities (MVPA) and PAL) was measured by a multi-sensor activity monitor (SenseWear Pro 3 Armband). Dyspnoea, complete pulmonary function tests, peripheral muscle strength and exercise capacity served as clinical characteristics. Additional information on material and methods is available in the online supplementary.

We found that physical activity was significantly lower in COPD compared to smoking controls (figure 1). Subjects with COPD with either mild symptoms of dyspnoea (mMRC 1), those with lower diffusion capacity (T_L,co), low 6 min walking distance (6MWD) or low maximal oxygen uptake (VO_2 peak) had significantly lower PALs (see online supplementary figure S2–S5). COPD subjects and smoking controls with lower levels of isometric quadriceps force did not show lower daily PALs. Multiple regression analysis identified 6MWD and T_L,co as independent predictors of physical activity in COPD (see online supplementary table S2).

Our data support the recent advice of Centers for Disease Control and Prevention that physical activity is an important vital sign, even in patients with mild disease.[3]

Several cross-sectional studies found that patients with an established diagnosis of mild-to-moderate COPD, recruited in hospital outpatient settings, were physically inactive compared to a (non-) smoking control group.[4 5] This is the first study that showed that early reduction in physical activity is already present in subjects with mild-to-moderate COPD who did not previously present to healthcare services (ie, preclinical stage). Of importance to clinicians is the finding that some clinical characteristics (mild symptoms of dyspnoea, low values of diffusion capacity and exercise capacity) may identify the inactive subjects. In this group, early therapeutic interventions such as activity counselling programmes could be helpful in preventing deterioration of the PALs, and by consequence, other clinical outcomes such as comorbidity and disease progression.[2] We conclude that the reduction in physical activity starts early in the disease, even when subjects are not yet diagnosed with COPD, especially in those

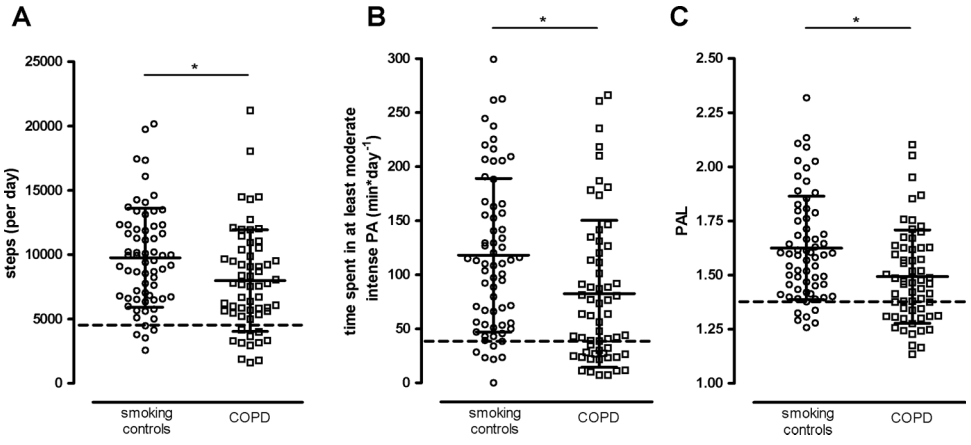

Figure 1 Daily physical activity levels (PAL) in subjects with and without chronic obstructive pulmonary disease (COPD); daily steps (A) 7986±2648 vs 9765±3078 steps, daily time spent in moderate-to-vigorous physical activity (MVPA) (B) 64 (27–120) vs 110 (55–164) min of MVPA and daily PAL (C): 1.49±0.21 vs 1.62±0.24 PAL. *p<0.05 COPD versus smoking controls.

with mild symptoms of dyspnoea, lower levels of diffusion capacity and exercise capacity.

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Contributors HVR contributed to the protocol development, collected the data, performed data analysis and wrote the manuscript. MH contributed to the protocol development, collected the data, performed data analysis and wrote the manuscript. HD contributed to the statistical analysis, assisted in the data collection and critically reviewed the manuscript. DL contributed to the protocol development, assisted in the data collection and critically reviewed the manuscript. CB, DL contributed to the protocol development, assisted in the data collection and critically reviewed the manuscript. MD contributed to the protocol development and critically reviewed the manuscript. RG contributed to the protocol development and critically reviewed the manuscript. WJ provided the study idea, contributed to the protocol development and critically reviewed the manuscript. TT provided the study idea, contributed to the protocol development and critically reviewed the manuscript.

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Competing interests None.

Ethics approval The study was approved by the local ethics committee (Medical Ethical Board of the University Hospitals Leuven, Belgium, approval number B32220096387).

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MATERIAL AND METHODS

Study design + participants

In this monocentric cross-sectional case-control study, subjects participating in a clinical trial (NELSON) were recruited between June 2009 and March 2012. NELSON is a Dutch-Belgian randomized lung screening trial which investigates whether 16-detector multi-slice computed tomography (CT) screening will decrease lung cancer mortality compared to no screening. Details of patient recruitment, inclusion and exclusion criteria are published elsewhere.[1] Briefly, all addresses of men and women (age 50-75 years) from 14 municipalities around Leuven (Belgium) were obtained (n=66,322) and 358 current or former smokers (age 50-75 years) responded to the questionnaires (general health, smoking exposure history, cancer history, etc.), met the eligibility criteria of the study, performed post-bronchodilator spirometry and were randomized into the CT screening or control group (no CT screening). From this study, 141 people (ex-) smokers agreed to participate of whom 62 subjects were identified as having spirometry proven COPD (cases) and 79 subjects did not have COPD (controls). Inclusion criteria of the study were age between 40 and 80 years, smoking history of at least 10 packyears and active smoking behavior till at least 10 years from the moment of enrollment. Patients were excluded if they had significant orthopedic or musculoskeletal problems which would interfere with their movement patterns, a recent diagnosis of cancer or respiratory disorders other than COPD (e.g. asthma). The study was approved by the local ethics committee (Medical Ethical Board of the University Hospitals Leuven, Belgium, approval number B32220096387) and all subjects provided written informed consent.

Study Procedures.

Symptoms of dyspnea, complete pulmonary function testing, physical exercise

testing, muscle force testing, and assessment of daily physical activity were assessed in all participants.

Symptoms of dyspnea

The modified Medical Research Council (mMRC) dyspnea scale rates the type and magnitude of dyspnea according to five grades (from mMRC 0 to mMRC 4) of increasing severity.[2]

Pulmonary function testing

Spirometric measurements (FEV_1, FVC), body plethysmographic measurements (inspiratory capacity (IC), functional residual capacity (FRC), residual volume (RV) and total lung capacity (TLC)) and single-breath diffusion capacity of the lung for carbon monoxide (T_L,co) were performed with standardized equipment (Whole Body Plethysmograph, CareFusion, Belgium) according to the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines.[3] Spirometric values were post-bonchodilator measurements, and all absolute values were expressed as percentage predicted of reference values.[4] Presence of COPD was defined by a post-bronchodilator FEV_1/FVC ratio <0.7 and post-bronchodilator FEV_1 was used to classify subjects into the appropriate GOLD (Global Initiative for Obstructive Lung Disease) stage according to the revised GOLD classification.[5] T_L,co was expressed as percentage of reference values.[6]

Physical exercise testing

Functional exercise capacity was determined by the six minute walking distance (6MWD).[7] Values were related to previously published reference values for the healthy Belgian population.[8] A symptom-limited incremental cycle ergometer test was conducted according to the ATS/ACCP statement on cardiopulmonary exercise testing to assess the maximal exercise capacity (VO_2 peak).[9] The values of peak

oxygen consumption (mean of last 30 seconds) were related to previously described reference values.[10]

Muscle force testing

Isometric quadriceps force (QF) was assessed with the subject seated on a dynamometer (Biodex Medical Systems, Inc., NY, USA), with the back straight, a 90° hip flexion and 60° knee flexion. Normal values had been previously reported.[11] Subjects performed 3 isometric maximal voluntary contractions for six seconds. The highest peak force value was used for analysis.

Assessment of daily physical activity

The SenseWear Pro Armband (BodyMedia, Inc., Pittsburgh, PA, USA) was worn for 7 complete (except during bathing and showering) and consecutive days to quantify physical activity. The device (85x54x20mm, 79g) is placed on the upper right arm and integrates information from a biaxial accelerometer with signals from non-invasive sensors measuring physical parameters such as changes in body temperature, near body ambient temperature, heat flux, and galvanic skin resistance. Together with individual characteristics including gender, age, height and body mass these variables are used to estimate energy expenditure (expressed as metabolic equivalents, METs) utilizing proprietary equations developed by the manufacturer. The number of daily steps, the daily time spent in moderate to vigorous physical activities (MVPA) and daily physical activity level (PAL, i.e. total energy expenditure divided by resting energy expenditure) were downloaded and analyzed using SenseWear Professional software 6.0. The time spent with an energy expenditure of >3 METS was considered as MVPA.[12] Total energy expenditure estimates of this activity monitor have been recently validated against the gold standard of doubly labeled water and indirect calorimetry in healthy adults [13] and patients with

COPD.[14, 15] A valid assessment was defined as at least 5 days (weekend days + at least 3 weekdays) of assessment during of at least 20 hours per day.[16]

Statistical analysis

Normal distribution was tested for all variables by a Kolmogorov-Smirnov test. Continuous variables were expressed as means with standard deviation (normal distribution) or as medians with interquartile range (skewed distribution). Categorical variables were expressed as proportions and testing between groups was done by a chi-square test. Comparisons between smoking controls and patients with COPD were performed by either a parametric (unpaired t-test) or non-parametric test (Wilcoxon-Mann-Whitney test). For the smoking control subjects the lower limit of normal was calculated as the value above which 90% of the control values were situated. The subjects with COPD below this lower limit of normal were defined as physically inactive.

Partial correlations in the subjects with (cases) and without COPD (smoking controls) were calculated to investigate whether any relationship existed between physical activity and lung function, muscle function or exercise capacity, after correcting for anthropometric variables (age, gender, weight and packyears) and season of assessment (daylight time, i.e. time from sunrise to sunset). Parameters of lung function (FEV_1, FEV_1/FVC ratio, IC/TLC ratio, RV/TLC ratio, T_L,co), muscle function (QF) and exercise capacity (6MWD and VO_2 peak) were divided into two categories by the median split method. After correcting for covariates (age, gender, BMI and season of assessment (daylight time)) physical activity levels (dependent variables) were compared between categories of dyspnea (mMRC), lung function, muscle function and exercise capacity by computing the least square means for the dependent variables using generalized linear models procedure. Finally, to investigate whether daily physical

activity is related to symptoms of dyspnea, lung function, muscle function and exercise capacity, a stepwise multiple regression analysis was performed in subjects with COPD, with age, gender, weight, packyears and daylight time (season) as potential covariates. All statistical analyses were performed with statistical software package SAS (version 9.3). The level of significance was 0.05 for all statistical tests.

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Table 1. Demographic and functional characteristics of study subjects.

Variable	Smoking controls (n=65)	COPD (n=59)
Age (years)	62 ± 7	63 ± 6
Sex (% male)	68	75
BMI	27.0 ± 3.8	26.9 ± 4.2
Packyears	35 ± 22	48 ± 22*
Current smokers (%)	50	49
Educational level (% high education)	54	49
Socio-economic status (% retired)	62	66
Season of assessment		
Winter (%)	30	31
Spring (%)	23	14
Summer (%)	16	17
Autumn (%)	31	38
FEV_1 (L)	3.04 ± 0.72	2.46 ± 0.65*
FEV_1 (% pred)	104 ± 15	85 ± 17*
FVC (L)	4.02 ± 0.88	4.03 ± 0.85
FVC (% pred)	110 ± 15	110 ± 15
FEV_1/FVC (%)	76 ± 4	61 ± 7*
GOLD stage I/II (n)		39/20
Group A (%)		100
FRC/TLC_p (%)	57 ± 10	69 ± 14*
RV/TLC (%)	36 ± 7	43 ± 7*
IC/TLC (%)	44 ± 7	38 ± 7*
T_L,co (% pred)	87 ± 13	78 ± 17*
mMRC 0/mMRC 1 (n)	36/27	28/30
QF (% pred)	92 ± 17	98 ± 21
6MWD (m)	609 ± 67	588 ± 86
6MWD (% pred)	92 ± 9	90 ± 11
VO_2 peak ($mL*min^{-1}*kg^{-1}$)	28.2 ± 7.2	25.4 ± 5.1*
VO_2 peak (% pred)	117 ± 33	107 ± 28*

BMI; Body Mass Index, FEV_1; forced expiratory volume in 1 second, FVC; forced vital capacity, Group A (revised GOLD classification); mMRC 0-1, GOLD 1-2 (former GOLD classification) and 0-1 exacerbations per year, FRC; functional residual capacity, $TLC_{(p)}$; (predicted) total lung capacity, RV; residual volume, TL_{CO}; diffusion capacity of the lung for carbon monoxide, mMRC; modified Medical Research Council (no subject reported mMRC>1), QF; quadriceps force, 6MWD; six-minute walking distance, VO_2 peak; peak oxygen uptake. *$p<0.05$ COPD versus smoking controls.

Table 2. Determinants of physical activity in subjects with COPD (n=59).

Variable	Factor	SEM	Partial R^2	R^2	P
STEPS					
Intercept	-9040	3160			
6MWD	23	6	0.24	0.24	0.0002
gender	-3832	1149	0.11	0.35	0.0016
T_L,co	591	282	0.04	0.39	0.04
Daylight time	4	2	0.02	0.41	0.12
MVPA					
Intercept	-177	56			
6MWD	0.33	0.09	0.23	0.23	0.0006
Daylight time	0.10	0.04	0.07	0.30	0.02
PAL					
Intercept	0.70	0.19			
6MWD	0.0008	0.0003	0.14	0.14	0.02
gender	-0.17	0.07	0.07	0.21	0.02
T_L,co	0.04	0.02	0.04	0.25	0.03
Daylight time	0.0003	0.0001	0.05	0.30	0.05

6MWD is expressed in meters, gender (0=female, 1=male), T_L,co in $mmol*min^{-1}*kPa$ and daylight time as minutes of daylight between sunrise and sunset.

FIGURE LEGENDS

Figure 1. Flow chart of the included study subjects, recruited from the Nelson trial.

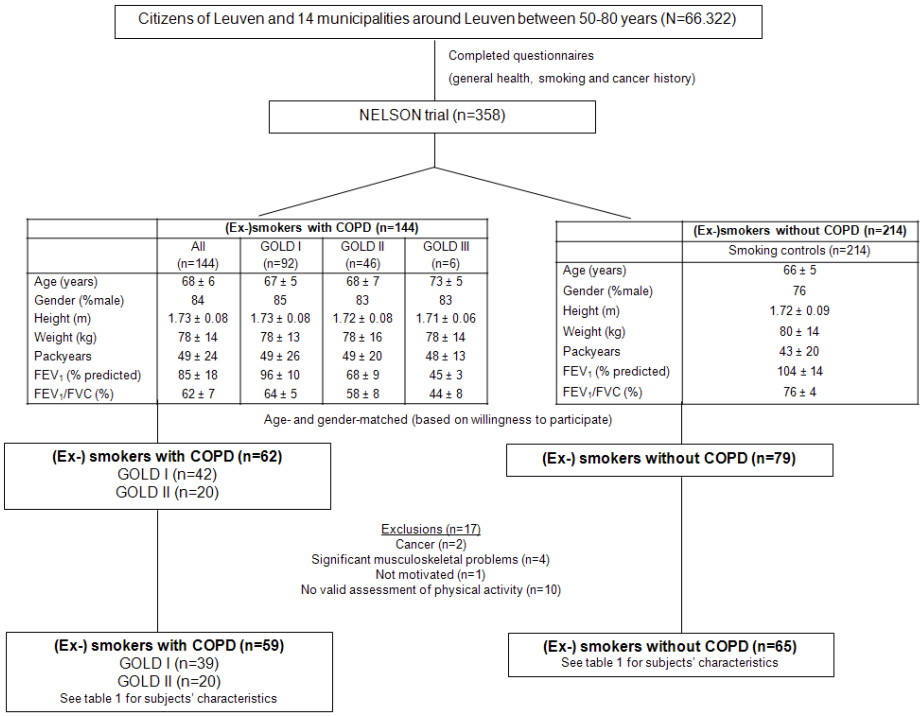

Figure 2. Daily physical activity in subjects with COPD and smoking controls with (mMRC1) and without (mMRC0) mild symptoms of dyspnea. *p<0.05 mMRC0 versus mMRC1.

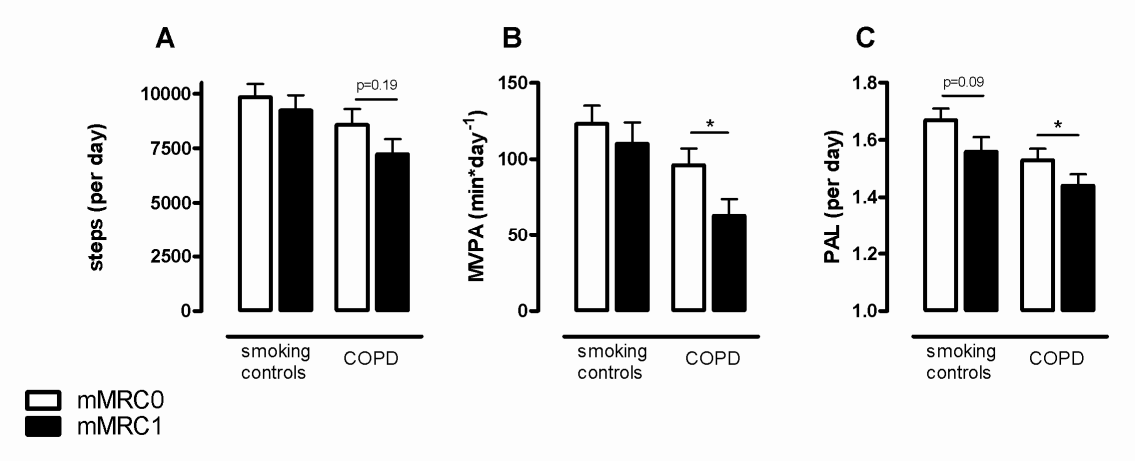

Figure 3. Daily physical activity levels (daily steps (A), daily time spent in moderate-to-vigorous intense physical activities (MVPA) (B) and daily physical activity level (PAL (C)) and a reduced diffusion capacity of the lung for carbon monoxide (T_L,co) in subjects with and without COPD. T_L,co below or equal to the median (7.7 mmol*min^{-1}*kPa or 88% predicted for smoking controls and 6.9 mmol*min^{-1}*kPa or 80% predicted for COPD) was defined as a reduced T_L,co. *p<0.05 T_L,co ≥ median versus T_L,co < median.

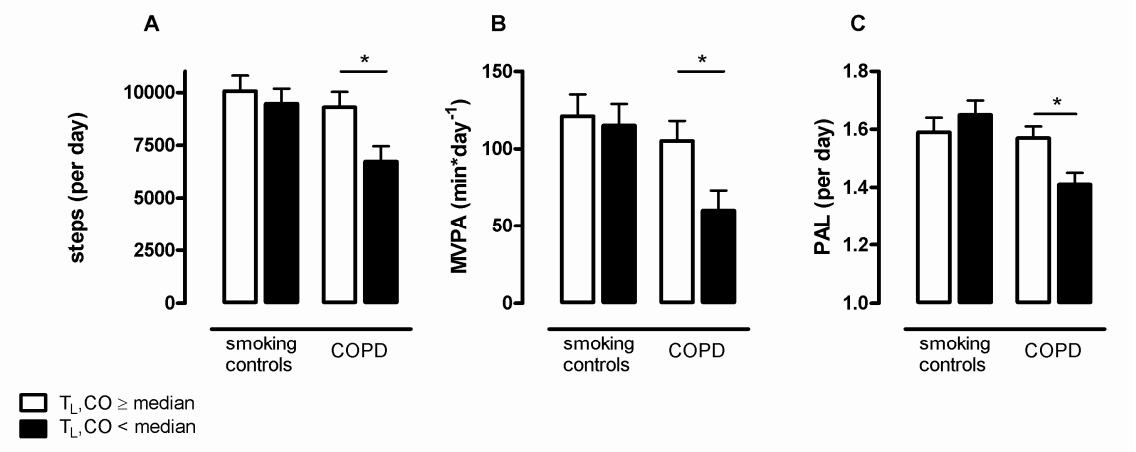

Figure 4. Daily physical activity levels (daily steps (A), daily time spent in moderate-to-vigorous intense physical activities (MVPA) (B) and daily physical activity level (PAL (C)) and a reduced six minute walking distance (6MWD) in subjects with and without COPD. 6MWD below or equal to the median (623 m or 93% predicted for smoking controls and 592 m or 90% predicted for COPD) was defined as a reduced 6MWD. *p<0.05 6MWD ≥ median versus 6MWD < median.

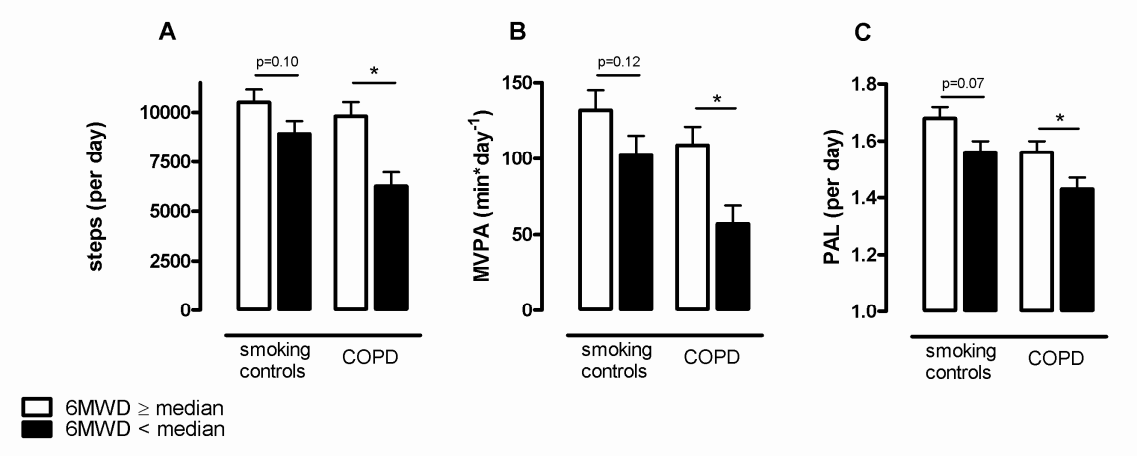

Figure 5. Daily physical activity levels (daily steps (A), daily time spent in moderate-to-vigorous intense physical activities (MVPA) (B) and daily physical activity level (PAL (C)) and a reduced peak oxygen consumption (peak VO_2) in subjects with and without COPD. Peak VO_2 below or equal to the median (2.23 $L*min^{-1}$ or 116% predicted for smoking controls and 2.00 $L*min^{-1}$ or 102% predicted for COPD) was defined as a reduced peak VO_2. *p<0.05 peak VO_2 ≥ median versus peak VO_2 < median.