

Physical activity impairment in depressed COPD patients

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Abstract

Introduction

Limited exercise tolerance is a cardinal clinical feature in COPD. Depression and COPD share some clinical features, such as reduced physical activity and impaired nutritional status. The aim of the present study was to evaluate maximal and daily physical activity, and the nutritional status of COPD patients affected or not by depression.

Methods

In 70 COPD outpatients daily and maximal physical activity were assessed by multisensor accelerometer armband, six-minute walking test and cardiopulmonary exercise test. Mental status, metabolic/muscular status, and systemic inflammation were evaluated through Hospital Anxiety and Depression scale, bioelectrical impedance analysis, and fibrinogen/C-reactive protein, respectively.

Results

Depressed patients (27% of the sample) showed a similar level of respiratory functional impairment, but a higher level of shortness of breath and a worse quality of life compared to non depressed patients ($P<0.05$). Specifically, they displayed a physical activity impairment consisting in a reduced number of steps per day, a lower peak of oxygen consumption, an early anaerobic threshold, and a reduced distance in the six minute walking test ($P<0.05$), but the same nutritional status compared to non depressed patients. In the multivariate analysis, a reduced breathing reserve, obesity, and a higher level of shortness of breath, but not depression, were found to be independent factors associated with a reduced daily number of steps.

Conclusions

Our study demonstrated that depressed COPD patients have a reduced daily and maximal exercise capacity compared to non depressed patients. This further remarks the potential utility of screening for depression in COPD.

Keywords: depression, COPD, exercise tolerance, dyspnea, nutritional status, C-PET

Introduction

Limited exercise tolerance, mainly related to airflow obstruction, is a cardinal clinical feature in chronic obstructive pulmonary disease (COPD). Perceived respiratory impairment, dyspnea, is the primary symptom limiting exercise in the majority of patients affected by COPD^{1, 2}. Persistent activity-related dyspnea often forces patients to adopt a sedentary lifestyle; inactivity, in turn, leads to generalized skeletal muscle deconditioning, further deteriorating the perceived quality of life. Severe activity-related dyspnea is, therefore, a major contributor to morbidity in COPD and an independent predictor of poor survival³.

The prevalence of depression in COPD patients varies significantly, from 8 to 80%, with mean values around 30%, higher when compared with gender- and age-matched healthy subjects⁴⁻⁷. A recent systematic review and meta-analysis performed by Atlantis E et al. elegantly demonstrated the bidirectional association between COPD and depression, with depression affecting the prognosis of COPD, and COPD increasing the risk of developing depression⁸. Numerous studies demonstrated a negative association between depression and anxious condition and amount of physical activity⁹⁻¹²; moreover, the link is bidirectional, since physical activity itself seems to improve depressive symptoms in people affected by depression when compared to no medical intervention¹³. Hence, the hypothesis that depression plays a role in exercise limitation in COPD patients is not clearly supported, with some studies demonstrating a relationship between depression and reduced exercise capacity in COPD^{14, 15}, and other studies rejecting it¹⁶⁻¹⁸. All the previous studies, however, evaluated exercise capacity with the use of field tests, such as the 6-min walking test (6MWT), which is relatively easy to perform but cannot be considered as sensitive as the cardiopulmonary exercise test, which defines the level of aerobic fitness on the basis of a comprehensive physiological evaluation¹⁹.

Malnutrition represents a common and often under-recognized comorbidity affecting COPD patients. Its prevalence ranges from 20% to 40% in outpatients and up to 70% in patients with acute respiratory failure or in those awaiting for lung transplantation²⁰. Malnutrition is associated with deterioration of physical performance and development of clinical complications. Survival studies have shown significantly higher mortality rates in underweight patients than in overweight patients affected by

COPD²¹. Depression similarly appears to be linked to poor nutritional status, characterized by poor dietary intake and low serum levels of nutrients²².

Therefore, COPD and depression appear likely to play a complementary role in the reduction of physical activity and in nutritional status impairment. The recognition of this dangerous link may be clinically important, as a potential target to improve patients' quality of life.

The present study was aimed at evaluating maximal and daily physical activity, nutritional status and body composition, pulmonary function, symptoms and quality of life of COPD patients according to the presence or not of depression. Secondary outcome was the study by multivariate analysis of variables related to a low daily physical activity.

Methods

Study subjects

Consecutive outpatients attending the Respiratory Unit of San Paolo Hospital (Milan, Italy) aged >40 years with a smoking history of >10 pack-years and a diagnosis of COPD according to the ATS/ERS guidelines were recruited²³. The study was approved by the local research ethics committee. All patients gave informed written consent.

Functional, symptoms assessment and comorbidities

Every patient underwent evaluation of clinical history, including number of exacerbations in the previous year, spirometry, body plethysmography, lung diffusion for carbon monoxide (DLCO), and arterial blood gas analysis. The level of dyspnea was estimated by using the Italian version of the modified Medical Resource Council (MRC) dyspnoea scale consisting of five statements regarding perceived breathlessness: from grade 1 (I only get breathless with strenuous exercise) up to grade 5 (I am too breathless to leave the

house)²⁴. Comorbidities were evaluated by Charlson index, with higher scores indicating more coexisting conditions²⁵.

Physical activity and cardiopulmonary fitness

Daily physical activity was measured by multisensor armband (SenseWear Pro Armband; BodyMedia, Inc., Pittsburgh, PA) worn 24 hours a day for 5 days. It incorporates a biaxial accelerometer that records the number of steps per day, and physiologic indicators of energy expenditure. We determined the physical activity level by dividing total daily energy expenditure by whole-night sleeping energy expenditure²⁶.

Cardiopulmonary exercise test (CPET) to maximum tolerance on an electromagnetically braked cycle ergometer was performed by a progressively increasing (personalized protocol) work rate. Gas exchange was analyzed (Cardiopulmonary Metabolic Cart, SensorMedics Vmax Spectra) at rest (3 min), during 2 min of unloaded cycling at 60 rpm, during exercise, and during final 3 min recovery period. ECG (12-lead) and cuff blood pressures were recorded. Respiratory gases were sampled continuously from a mouthpiece, and minute ventilation (VE), CO₂ output (VCO₂), O₂ consumption (VO₂), respiratory exchange ratio, and other exercise variables were calculated breath-by-breath by computer, interpolated second-by-second, and averaged at 10-s intervals. The anaerobic threshold (AT) was derived by V-slope analysis. O₂ pulse (an index of changes in stroke volume) was determined by standard methods¹⁹. Peak VO₂ was determined by the highest VO₂ achieved during exercise. The breathing reserve (BR) was calculated as absolute value (in liters) by the difference between the maximum VE reached during the CPET and the maximum voluntary ventilation (calculated for each patient as FEV₁ multiplied by 35)²⁷. N-terminal pro-B-type natriuretic peptide (pro-BNP) was used as a systemic biomarker of heart failure²⁸.

The six-minute walking test (6MWT) was performed indoors, along a flat, straight, 30 m walking course supervised by a trained operator according to ATS guidelines²⁹. Transcutaneous oxygen saturation and walked distance were recorded.

Metabolic, nutritional status, systemic inflammation and anemia

Body mass index (BMI), fat-free mass index (FFMI), and body fat-mass index (BFMI) were measured by bioelectrical impedance analysis (BIA, SoftTissue Analyzer, Akern Bioresarch, Firenze, Italy). Patients were considered as having an abnormal nutritional status in case of nutritional depletion (BMI of 21 kg/m² or less or a FFMI of 16 kg/m² or less in men and 15 kg/m² or less in women ³⁰), or in case of obesity (BMI ≥ 30, or BMFI ≥ 8.2 in men, and ≥11.8 in women ³¹). Patients underwent blood analysis including cholesterol levels (both HDL and LDL), triglycerides and albumin; anemia was defined as a hemoglobin level below 13 g/dl ³². C-reactive protein (CRP), and fibrinogen served as markers of systemic inflammation.

Depression, anxiety, and quality of life

Depression and anxiety levels were assessed with the Hospital Anxiety and Depression scale (HAD), which is self-reported and has been extensively used to screen psychiatric morbidity ³³ in a diverse range of clinical groups, including asthmatic and COPD patients ³⁴⁻³⁷. It is comprised of two parts, the first with seven questions related to anxiety and the second with seven questions related to depression. The maximum score for each domain (i.e. anxiety and depression) is 21; a score of ≥8 on either part is used as a threshold for diagnosing depression and anxiety ³³.

The Italian version of the St George's Respiratory questionnaire (SGRQ) comprises 50 items and 76 weighted responses divided into three subscales: symptoms, activity and impact; it was used for the evaluation of quality of life (QoL). Scores range from 0 to 100%, 0 representing the best possible score and 100% the worst ³⁸.

Statistical analysis

The results are shown as mean \pm standard deviation (SD), unless otherwise stated. The sample size was tailored on the multivariate linear regression analysis (shown below), in order to include at least 6 predictor variables. On the basis of a power calculation, it was estimated that, with an expected prevalence of depression in COPD of 25%, the enrollment of 70 patients allows to have an 80% statistical power and a 5% significance level of detecting a difference in 6MWT distance of 60 meters. According with the number of enrolled patients, a Kolmogorov-Smirnov test was performed before the data analysis in order to examine the data distribution of the overall sample. This test documented that all the evaluated continuous variables were distributed in a normal way, therefore permitting the use of parametric tests for data management. Continuous variables were compared using paired samples Student's t-test, whilst Fisher's test served for categorical data.

Multivariate linear regression analysis was performed using the number of steps per day as the dependent variable, to evaluate if depression itself is an independent factor associated with reduced physical activity. A stepwise approach to model building was applied, including in the model the variable identified by univariate analysis, comparing patients with a low or high physical activity (using as cut-off the 50th percentile of the distribution of steps per day).

All tests were two-sided, and p-values lower than 0.05 were considered statistically significant. Statistical tests were performed using the Statistical Package for Social Sciences (version 19.0; SPSS, Chicago, USA).

Results

Patient characteristics, pulmonary impairment, history, and quality of life are depicted in Table 1. Nineteen patients (27% of the sample) showed a significant high score of depression.

Features of depressed patients

A greater percentage of depressed patients were women compared to non-depressed patients, with a concomitant higher score of anxiety. Despite a similar level of respiratory functional impairment in terms of forced expiratory volume in one second (FEV_1), inspiratory capacity, DLCO and gas exchange, and a similar number of comorbidities, they showed a higher level of shortness of breath, and a statistically significant and clinically relevant worse quality of life (Table 1).

No difference was found between depressed and non depressed patients in terms of nutritional status, with a similar prevalence of obesity and nutritional depletion in the two groups (Table 2). Also, fat-free mass index (FFMI), and body fat-mass index (BFMI) levels were similar in patients with and without depression. However, depressed patients showed an impaired physical activity and maximal performance, as demonstrated by a reduced number of steps per day, a lower peak of oxygen consumption, a precocious anaerobic threshold, and a reduced walked distance in the six-minute walking test (Table 2, and Figure 1). On the other hand, depressed patients showed the same time of sleep and length of physical activity compared to non-depressed patients. Finally, we did not find any significant difference between depressed and non depressed patients in terms of systemic inflammation evaluated by CRP and fibrinogen (Table 2).

Features of patients with a low daily physical activity

For this univariate analysis we used the 50th percentile that resulted in a threshold of 6330 steps per day. Patients with a low physical activity (less than 6330 steps per day) showed a higher score of depression (HAD depression score 5.9 ± 4.0 vs. 3.7 ± 3.8 , $P=.022$), a lower breathing reserve (11.6 ± 20.9 vs. 25.3 ± 30.2 meters, $P=.031$), a lower inspiratory capacity (71 ± 16 vs. 81 ± 25 % of predicted values, $P=.049$), a higher frequency of obesity (34% vs. 11%, $P=.044$), a higher level of shortness of breath (MRC scale score: $1.6 \pm .8$ vs. $1.1 \pm .7$, $P=.015$), and a higher number of exacerbations in the previous year (0.9 ± 0.9 vs. 0.51 ± 0.9 , $P=.049$).

Multivariate linear regression analysis found three independent variables with significant effect on the number of steps per day: a reduced breathing reserve, obesity, and a higher level of shortness of breath (Table 3).

Discussion

To the best of our knowledge this is the first study carried out in COPD patients specifically designed to explore whether depressed patients have a concomitant reduction in physical activity, evaluated comprehensively by cardiopulmonary exercise test, multisensor armband and six-minute walking test. Depressed patients displayed a reduced daily and maximal physical activity, as demonstrated by a reduced number of steps per day, maximal oxygen consumption, a precocious anaerobic threshold, and a reduced walked distance at the 6MWT, despite similar levels of functional and gas exchange impairment compared to non depressed COPD patients. Moreover, depressed patients had a higher level of shortness of breath and a clinically significant worse quality of life. We did not find any significant difference between depressed and non depressed patients in terms of nutritional status, with similar levels of BMI, fat-free mass index, body fat-mass index cholesterol (both HDL and LDL), triglycerides and albumin in the two groups. Finally, lung function impairment (breathing reserve), nutritional status (obesity), and symptoms (level of dyspnea), but not depression, resulted to be independent factors correlated to number of steps per day.

The prevalence (27%) and general features of COPD patients with depression found in our study (more often females, with a worse quality of life and a higher level of shortness of breath) are similar to those of the ECLIPSE study that included more than 1700 patients³⁹. Moreover, our results correlate to those obtained by a previous study by Al-shair K et al⁴⁰ who, in a cohort of 122 patients with stable COPD, did not find any significant difference between patients with and without depression in terms of muscle wasting, but a significant difference in terms of exercise capacity evaluated by 6MWT. The correlation between depressive symptoms and a poor 6MWT performance was also demonstrated in the ECLIPSE study

^{15, 39}. The six-minute walking test, however, is a tool that roughly assesses maximal physical activity, and cannot be used to predict nor daily nor maximal physical activity. Our study, in comparison with the previous ones, evaluated these parameters by current gold standards: cardiopulmonary exercise testing and multisensor armband. The recorded information permitted a comprehensive evaluation of COPD patients with depression, that couple a reduced daily activity with signs of physical deconditioning, such as a reduced anaerobic threshold. This is particularly dangerous in COPD patients, as the introduction of the vicious circle between shortness of breath, reduced physical activity, and body deconditioning can significantly affect mortality. The early anaerobic threshold we found in depressed patients is particularly interesting, since it reflects physical deconditioning, which may be due to, and may lead to depression at the same time. It is noteworthy that exercise is of proven efficacy in the improvement of respiratory disability in COPD and seems to improve depressive symptoms in subjects diagnosed with depression when compared to no treatment ¹³.

In contrast with the ECLIPSE study we did not find any significant difference between depressed and non depressed patients in terms of age and severity of obstruction, expressed by FEV1 ³⁹. This apparent discrepancy is probably due to the lower number of enrolled patients of our study; however, the difference found by Hanania N et al in the ECLIPSE study, even if statistically significant, is very little and probably not so clinically significant, since depressed patients were only 2 years younger, with values of FEV1 on average 3% lower than non depressed patients ³⁹.

In accordance with our results, Watz J et al. ⁴¹, in a cross-sectional study conducted on 70 patients, found that depression itself is not an independent factor correlated with daily physical activity. Interestingly, Watz J et al. ⁴¹ found that systemic inflammation and left cardiac dysfunction were associated with reduced physical activity. In our study, even if left ventricular function was not assessed, we did not find any significant correlation between a reduced number of steps per day and the values of pro-BNP, a biomarker of heart failure. On the other hand, the discrepancy in terms of systemic inflammation could be due to the features of enrolled patients. In fact, the group studied by Watz J et al. presents a high rate of current smokers (42%), compared to the 18% of our study population, and there is a well known role of

active smoking itself in both CRP and fibrinogen ⁴². Finally, the lack of a significant association between depression and systemic inflammation has been confirmed in the large population of the ECLIPSE study ³⁹, in which no significant altered levels of fibrinogen and CRP were detected in depressed patients.

The correlation observed between physical activity and an impairment of the mechanical properties of the lung appears quite convincing, since the multivariate analysis found two parameters independently correlated to the number of steps per day: a reduced inspiratory capacity and breathing reserve. In our study obesity resulted as a risk factor for reduced daily activity, such as previously demonstrated in general population ⁴³. Similarly, Watz H et al. found that daily activity in COPD is reduced in patients with mild functional impairment, and that both BMI and the level of shortness of breath influence the level of physical activity ⁴¹. How to explain the fact that depression is correlated to a reduced daily and maximal physical activity, but is not an independent predictor of daily activity? This result, in our opinion, highlights the complexity of reduced exercise tolerance in COPD, which is mainly related, as this study demonstrated, to lung hyperinflation, but also depends on many other factors; in particular, we found nutritional status and the level of shortness of breath. Depression itself is associated with an increased level of shortness of breath and a worse perceived quality of life, as previously demonstrated ^{4, 39}. Hence, even if the correlation between depression and impaired physical activity appears consolidated, the reason for which COPD patients have a limited daily activity is more complex and mediated by diverse factors, such as the functional impact of the respiratory disease, the perceived level of symptoms and quality of life impairment. Finally, as previously discussed, depression can be interpreted as the effect, rather than the cause of a reduced daily activity.

Our study has limitations that need to be addressed. Firstly, since this is a cross-sectional study no causality or directionality of the findings can be inferred, a limit common to all the other studies conducted on the same topic; moreover, a recent sophisticated systematic review and meta-analysis concluded that there is a bidirectional association between COPD and depression ⁸. Secondly, we studied a limited number of patients, as compared to other previous studies. This is due to the necessity of carrying out cardiopulmonary exercise test and 5-days multisensor armband evaluation, tests that however represent

the true originality of the present paper. Thirdly, we did not investigate appetite and socioeconomic status, parameters that could have helped us in the evaluation of the reason for a potential difference in terms of nutritional status between depressed and non depressed patients that, however, was not find in our study. Finally, depression has been evaluated with one simple questionnaire and not with a structured interview or additional questionnaires. HAD scale has been successfully used in several clinical groups; furthermore, Lavoie et al.⁴⁴ confirmed the accuracy of questionnaires, by comparing the obtained results with those of a structured interview⁴⁴

Conclusions

The present study demonstrates that depressed COPD patients have a significant reduced daily and maximal exercise capacity, but not an impaired nutritional status. Specifically, a precocious anaerobic threshold suggests the presence of physical deconditioning in these patients, therefore supporting the use of therapies aimed at improving exercise capacity which have already demonstrated their utility in COPD and may also improve mood profile in patients with depression. This study remarks suggests the potential utility of screening for depression in COPD.

FIGURE 1. Differences in exercise capacity between depressed (n=19) and non depressed (n=51) patients. In 1.a, the number of steps per day, recorded by a multisensor armband; in 1.b the distance expressed in meters walked during the 6 minutes test; 1.c and 1.d refer to the highest value of oxygen consumption (VO_2), and the anaerobic threshold, respectively, obtained during cardiopulmonary exercise test.

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Table 1. Anthropometric, clinical, pulmonary function data, and quality of life of patients studied (entire population, and classified as affected or not by depression).

	All patients (n=70)	No depression (n=51)	With depression (n=19)	P
Females, n (%)	18 (26)	9 (18)	9 (47)	.012
Age, years	71±6	71±7	72±5	.412
Pack-years of smoking, n	48±27	48±27	48±26	.697
Current smokers, n (%)	13 (18)	9 (21)	4 (18)	.494
Depression HAD score	5±4	3±2	10±3	<.001
Anxiety HAD score	4.7±2.9	3.9±2.8	6.9±1.8	<.001
Anxiety, n (%)	18 (26)	9 (18)	9 (47)	.028
FEV1, %	63±14	63±15	61±11	.496
Inspiratory capacity, %	75±21	76±21	73±21	.600
DLCO, %	69±21	70±23	66±16	.459
DLCO/VA, %	63±16	62±19	65±9	.548
Exacerbation previous year, n	.73±.9	.8±1.0	.5±.6	.262
Breathlessness, MRC score	1.3±.8	1.2±.8	1.8±.6	.003
PaO₂, mmHg	75±8	74±8	77±8	.180
PaCO₂, mmHg	40±5	41±5	39±3	.143
SGRQ, total score	30.4±13.7	25.2±11.1	44.3±9.9	<.001
SGRQ, symptoms score	35.1±18.5	30.3±18.6	48.9±16.0	<.001
SGRQ, impact score	19.1±14.3	14.3±11.5	31.9±13.2	<.001
SGRQ, activity score	47.7±18.3	41.4±17.0	64.3±9.0	<.001
Charlson index, score	2.0±1.4	1.9±1.4	2.3±1.4	.300

Data are shown as mean±SD. Depression and anxiety were defined as an Hospital Anxiety Depression score for depression, and anxiety ≥8. DLCO: lung diffusion for carbon monoxide; VA: alveolar volume; SGRQ: MRC: modified Medical Resource Council dyspnoea scale; St George's Respiratory questionnaire. **In bold:** difference between patients with and without depression statistically significant (P<0.05).

Table 2. Nutritional status, physical activity, cardiopulmonary fitness, and systemic inflammation of patients studied (entire population, and classified as affected or not by depression).

	All patients	No depression	With depression	P
	(n=70)	(n=51)	(n=19)	
Body Mass Index, Kg/m²	27.6±3.9	27.1±3.9	28.7±3.8	.150
Fat-free mass index, Kg/m²%	18.6±1.8	18.5±1.8	18.8±1.9	.610
Body fat-mass index, Kg/m²%	8.0±2.6	7.6±2.6	8.9±2.6	.060
Obesity, n (%)	16 (23)	10 (20)	6 (32)	.343
Nutritional depletion, n (%)	3 (4)	3 (6)	0 (0)	.557
Hemoglobin, gr/dl	14.9±1.5	15.0±1.6	14.7±1.4	.530
Albumin, gr/dl	4.4±.2	4.4±.2	4.3±.2	.124
Cholesterol Total, mg/dl	190±56	193±38	183±25	.298
Cholesterol HDL, mg/dl	55±10	56±11	53±9	.388
Cholesterol LDL, mg/dl	135±35	137±39	129±25	.439
Triglycerides, mg/dl	138±108	138±114	139±57	.974
Glucose, mg/dl	104±15	102±15	109±15	.081
Physical activity level	1.47±.15	1.49±.16	1.43±.10	.184
Steps per day	6436±2595	6950±2431	5055±2576	.006
Time >3 METs, mins/day	52±33	56±32	43±35	.144
Sleep time, mins/day	350±72	350±76	351±52	.950
Time lying, mins/day	440±86	440±92	442±69	.931
Peak O₂ consumption, ml/Kg/min	19±5	21±5	16±3	<.001
Anaerobic threshold, % peak	72±19	76±13	62±26	.027
Breathing reserve, liters	18±27	22±28	9±19	.081
Work max, watts	80±30	84±32	70±20	.178
O₂-pulse, % predicted values	112±22	113±20	109±26	.495
Pro-BNP, pg/ml	152±201	136±213	159±39	.260
6MWT distance walked, meters	378±93	393±92	337±85	.023
6MWT SO₂ drop, %	2.6±2.3	2.6±2.4	2.5±2.2	.898

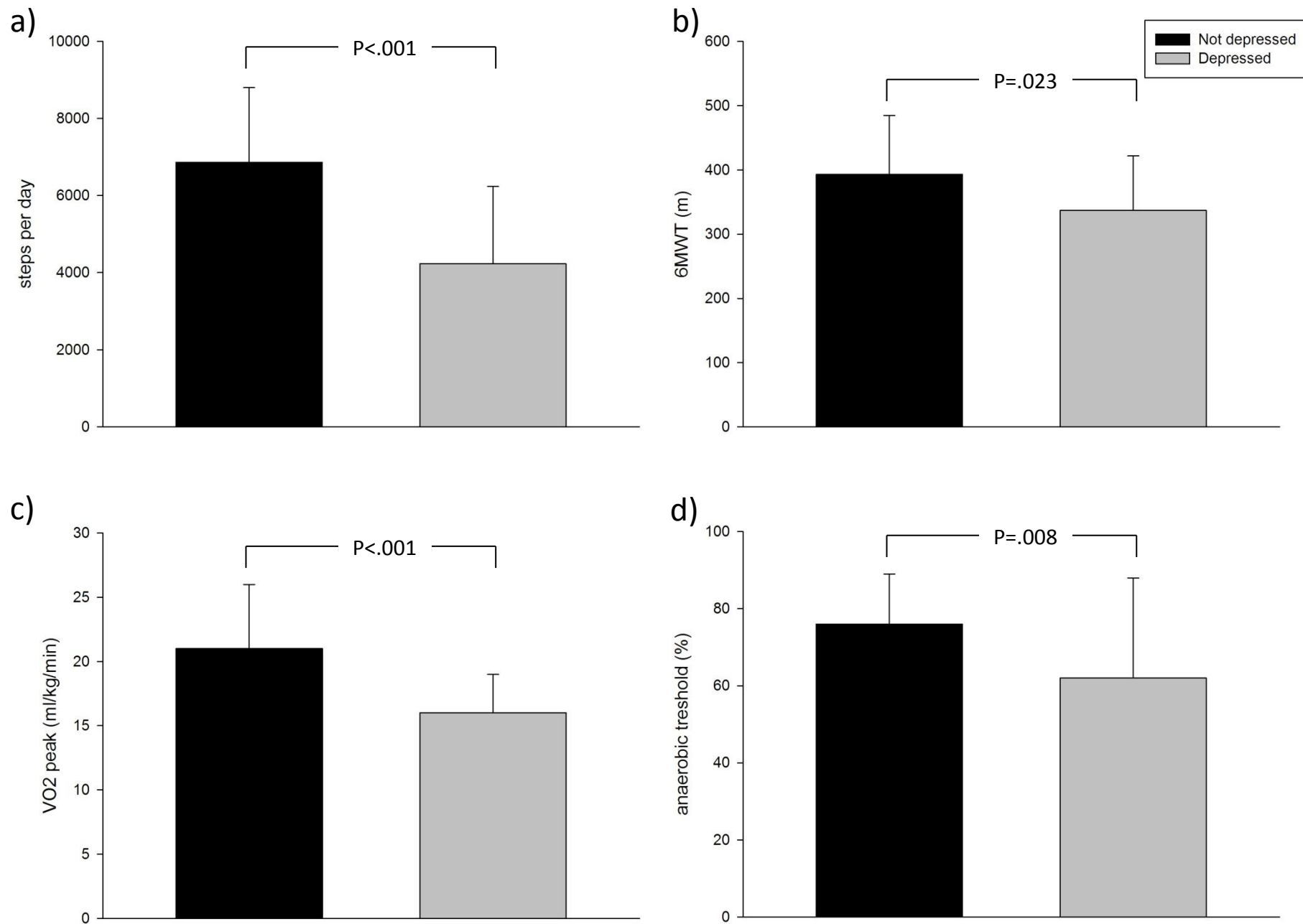
C-reactive protein , pg/ml	9.3±16.0	10.5±19	5.8±3.9	.279
Fibrinogen , mg/dl	372±68	378±74	358±48	.303

Data are shown as mean±SD. Depression was defined as an Hospital Anxiety Depression score for depression ≥8. HDL: high-density lipoprotein; LDL: low-density lipoprotein. Physical activity level: ratio total daily energy expenditure and whole-night sleeping energy expenditure; METs: standard metabolic equivalents; breathing reserve: difference between the maximum ventilation reached during the cardiopulmonary exercise test and the maximum voluntary ventilation (calculated as FEV₁ multiplied by 35); Pro-BNP: N-terminal pro-B-type natriuretic peptide; 6MWT SO₂ drop: difference between final and initial SO₂. **In bold**: difference between patients with and without depression statistically significant (P<0.05).

Table 3. Predictors of steps per day in a multivariate linear regression analysis.

Predictive parameters	Standardized regression coefficients			
	Beta	P	R ²	R ² Change
Depression HAD score	-.106	.836		
Breathing reserve , liters	.406	<.001	.163	.163
Inspiratory capacity , %	.057	.885		
Obesity	-.371	.001	.292	.129
Breathlessness , MRC score	-.243	.026	.347	.055
Exacerbation previous year	-.023	.830		

HAD: Hospital Anxiety Depression scale; breathing reserve: difference between the maximum ventilation reached during the cardiopulmonary exercise test and the maximum voluntary ventilation (calculated as FEV₁ multiplied by 35); MRC: modified Medical Resource Council dyspnoea scale. **In bold**: parameters independently correlated with the number of steps per day (P<0.05).



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