ORIGINAL RESEARCH

Depression, body mass index, and chronic obstructive pulmonary disease – a holistic approach

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Background: Several clinical studies suggest common underlying pathogenetic mechanisms of COPD and depressive/anxiety disorders. We aim to evaluate psychopathological and physical effects of aerobic exercise, proposed in the context of pulmonary rehabilitation, in a sample of COPD patients, through the correlation of some psychopathological variables and physical/pneumological parameters.

Methods: Fifty-two consecutive subjects were enrolled. At baseline, the sample was divided into two subgroups consisting of 38 depression-positive and 14 depression-negative subjects according to the Hamilton Depression Rating Scale (HAM-D). After the rehabilitation treatment, we compared psychometric and physical examinations between the two groups.

Results: The differences after the rehabilitation program in all assessed parameters demonstrated a significant improvement in psychiatric and pneumological conditions. The reduction of BMI was significantly correlated with fat mass but only in the depression-positive patients.

Conclusion: Our results suggest that pulmonary rehabilitation improves depressive and anxiety symptoms in COPD. This improvement is significantly related to the reduction of fat mass and BMI only in depressed COPD patients, in whom these parameters were related at baseline. These findings suggest that depressed COPD patients could benefit from a rehabilitation program in the context of a multidisciplinary approach.

Keywords: COPD, depression, aerobic exercise, BMI

Introduction

According to the World Health Organization (WHO), depression was ranked as the third leading cause of the global burden of disease in 2004 and will move into the first place by 2030. Worldwide, the fifth contributor to the burden of disease in 2020 is predicted to be COPD.[1,2]

As defined by American Thoracic Society (ATS) and European Respiratory Society (ERS), COPD is a preventable and treatable disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. It consists of the association of chronic bronchitis and emphysema. Chronic bronchitis is defined clinically as chronic productive cough for 3 months in each of 2 successive years in a patient in whom other causes of productive chronic cough have been excluded. Emphysema is defined pathologically as the presence of permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis.[3]

Several clinical studies show high rates of anxiety (21%–96%)[4] and affective (mostly depressive) disorders (27%–79%) in COPD,[5,6] which can affect prognostic evolution in terms of compliance, disability, and mortality.[7] It is not easy to diagnose depression in COPD patients because of overlapping symptoms between COPD and depression. Severe COPD could lead to somatic symptoms that are difficult to distinguish from depressive symptoms: eg, change in appetite/weight versus tearfulness/depressed appearance; sleep disturbances versus social withdrawal; fatigue or loss of energy versus brooding/pessimism; and diminished ability to think or concentrate versus lack of reactivity to environmental events. The validity of the International Classification of Diseases (ICD)-10 and *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-5 criteria for depression, in fact, may to a certain degree be questioned, because it is difficult to decide when somatic symptoms are secondary to depression and when they are secondary to COPD.[8] Additional variables that have potential to confound the association between COPD and depression regard some common risk factors, including the subject's demographic characteristics (age, sex, race/ethnicity, and marital status), education, body mass index (BMI), alcohol consumption, tobacco use, socioeconomic status (income), respiratory symptoms (dyspnea and difficulty with walking), and comorbid chronic conditions such as heart disease, stroke, diabetes, arthritis, hypertension, congestive heart failure, and cancer.[9]

The nature of the relationship between COPD and depression is not clear. However, it is well documented that depressed patients show a markedly elevated rate of cigarette smoking,[10] which is the most important risk factor for COPD. It has been also postulated that (mild) hypoxia – that is also present in COPD patients – can induce central neurobiological changes that predispose to depression and suicide.[11] Furthermore, in a study with a large sample, a relevant percentage of COPD patients entering pulmonary rehabilitation experienced clinically relevant symptoms of anxiety and depression.[12]

However, it could be supposed that both COPD and depression are the clinical manifestations of a common underlying pathophysiologic process. Indeed, data in the literature show that COPD and depression might not be "comorbid" conditions per se, but rather both are pathophysiologically related with a common substrate.[13–26]

Some authors suggest considering COPD as a "chronic systemic inflammatory syndrome" rather than a respiratory disease associated with extrapulmonary symptoms (including neurocognitive deficits, depression, anxiety, sleep disturbance, and other non-mental chronic disorders, such as coronary and peripheral artery diseases, anemia, osteoporosis, and rheumatoid arthritis).[14]

Some characteristics commonly observed in COPD patients, like obesity,[27] are indeed associated with inflammation processes related to depression and anxiety,[28] suggesting a complex bidirectional association between adiposity and depression.[26] In this field, as suggested by some authors, the reduction of adiposity through physical exercise seems related to significant changes in depressive symptoms.[29] As a consequence, ATS and ERS guidelines have emphasized the importance of pulmonary rehabilitation for patients with COPD.[30]

Several authors have indeed shown that there is a strong correlation among physical activity, adiposity, and mental health: several data have suggested that aerobic exercise shows significant effects, comparable to pharmacotherapy[31–33] and to psychotherapy,[34] on reducing depressive symptomatology.[35]

Coventry et al specifically demonstrated that structured exercise training significantly reduces both symptoms of depression and anxiety in people with COPD; furthermore, they showed that structured exercise training is more effective than other, complex psychological, behavioral and lifestyle interventions previously thought to improve mental health in people with COPD.[36]

Pulmonary rehabilitation shows poor effects on lung physiology (eg, ventilation parameters); nevertheless, it improves dyspnea, performance, anxiety, depressive symptoms, and quality of life (QoL).[37–42] It also seems to decrease secretory function of adipocytes, resulting in reduction of their volume measured through fat mass.[43] In this regard, although BMI is widely used as an indirect parameter to assess adiposity, it has been demonstrated that BMI would have a poor correlation with fat mass, which probably represents a more accurate measure.[43]

Considering the impact of aerobic exercise on anxious and depressive symptomatology, physical performance, QoL, and adiposity (assessed with BMI and fat mass), the primary aim of this study was to evaluate the effects of aerobic exercise, proposed in the context of pulmonary rehabilitation, through the correlation of psychopathological variables (depressive and anxious symptoms) and physical/pneumological parameters. The secondary endpoint regards the evaluation of potential improvement in QoL and in cognitive performance.

Materials and methods

This prospective cohort study was carried out in pneumology and psychiatry wards in the University Hospital Policlinico-Vittorio Emanuele of Catania, Italy from January to June 2012. The study was approved by the local ethical committee of the Policlinico "G. Rodolico" University Hospital, in accordance with the code of ethics of the World Medical Association, and written informed consent was obtained by all participants.

Inclusion criteria were diagnosis of COPD and eligibility to perform pulmonary rehabilitation, according to ATS and ERS guidelines.[44]

Exclusion criteria were indication for restoring treatment of airway patency and current psychopharmacological treatment (including sleeping pills).

Fifty-two consecutive subjects (46 males and six females) were enrolled, with a mean age of 71.5±6.29 years and a mean school education of 8.08±3.21 years.

Enrolled patients started a 6-week rehabilitation protocol, consisting of lower limb/limbs (treadmill and exercise bike) and upper art (arm ergometer Davenbike®) training, as well as calisthenic exercises with increasing intensity from a minimum of 80% to a maximum workload for lower arts in a minimum time.

As proposed by the lung specialists in the pneumology ward of our university hospital, training sessions went on for 2 hours over 5 days a week and were supervised by two physiotherapists and a lung specialist. To exclude potential bias, no change in diet regime was carried out during the full duration of the trial.

Patients were evaluated at first access to pulmonary rehabilitation outpatient wards in order to assess inclusion and exclusion criteria.

For eligible patients, psychometric assessment, completion of the preliminary investigation, and admission in the rehabilitation program were performed. The assessment, measured both at baseline and at the end of the 3-month rehabilitation program, consisted of spirometry with bronchodilator test, walking test (6-minute walk test [6MWT]), BMI, Medical Research Council (MRC) dyspnea scale, impedentiometry, motor and metabolic evaluation by SenseWear Armband (for 3 consecutive days), Hopkins Symptom Checklist 90 (SCL-90), Hamilton Depression Rating Scale (HAM-D), Hospital Anxiety and Depression Scale (subscale HADS-A for anxiety; subscale HADS-D for depression), and State-Trait Anxiety Inventory (STAI-1 and STAI-2). Cognitive functions were also evaluated using Raven's Colored Progressive Matrices (CPM), Rey Auditory Verbal Learning Test (RAVLT), Clock Drawing Test (CDT), and Trail Making Test parts A, B, and BA (TMT-A, TMT-B, and TMT-BA).

According to the HAM-D score (cutoff =8), the total sample was divided into two subgroups: depression-positive (D) and depression-negative (ND) subjects.

Continuous variables were compared using the Student's t-test and the Mann–Whitney U-test. Correlations were evaluated using Spearman's coefficient. Categorical variables were compared by chi-square test. A two-tailed test was used to assess statistical significance; a P-value of <0.05 was considered significant and a P-value of <0.01 was considered highly significant. Statistical analysis was performed using the Intercooled Stata 8 for Windows software (StataCorp LP, College Station, TX, USA).

Results

The descriptive analysis of psychometric and pneumological parameters at baseline and at the end of the rehabilitation program (at the end of month 3) are presented in Table 1.

Data show that improvement in all pneumological and respiratory parameters was statistically significant, except for Tiffeneau index.

The sample was divided into two subgroups consisting of 38 D and 14 ND subjects according to HAM-D.

The mean and standard deviation of psychometric and pneumological parameters at baseline and month 3 in both patient subgroups are shown in Table 2. We did not find a statically significant difference between the two subgroups in age, lung function, and baseline body composition.

Regarding the mean BMI at baseline, the D subgroup was overweight (24/38 patients, =63%, had a mean BMI 28.37±6.80) and the ND subgroup was normal weight (4/14 patients, =28%, had a mean BMI 24.96±4.1) (Figures 1 and 2), according to WHO criteria,[45] even if the absolute difference in BMI between the two subgroups was not statistically significant. Pneumological and psychological parameters overlapped except for HAM-D (P=0.002), HADS-A (P=0.03), SCL-90 (P=0.02), and TMT-A (P=0.02): these differences disappeared at 3 months. At baseline 73% of subjects (38/52) exceeded the cutoff for depression on the HAM-D (D subgroup). At month 3, the rate of D subjects was reduced from 73% to 7.7% (4/52, odds ratio 6.6, P=0.0002). The improvement in almost all other psychological and medical/pneumological parameters was also significant both in the D and ND subgroups at the end of the study.

We compared reported differences following the rehabilitation treatment between the D and ND subgroups

Table 1 Descriptive and paired comparison analysis of psychometric and pneumological parameters at baseline and at 3 months in the total sample of patients with COPD in a pulmonary rehabilitation program

Parameters	Baseline		3 months		Variations		P-value
	Median	SD	Median	SD	Median	SD	
HAM-D	11.31	6.31	3.88	3.70	−7.42	5.99	<0.0001
HADS-A	5.73	2.38	2.54	2.04	−3.19	2.58	<0.0001
HADS-D	8.15	3.91	3.19	2.54	−4.96	3.26	<0.0001
STAI-1	40.73	9.00	30.50	6.09	−10.23	9.27	<0.0001
STAI-2	40.96	8.19	29.85	7.44	−11.12	8.94	<0.0001
SCL-90	0.72	0.31	0.30	0.22	−0.42	0.28	<0.0001
TMT-A	67.73	22.32	54.50	14.65	−13.23	21.24	0.0089
TMT-B	200.40	81.68	132.50	49.86	−67.88	65.89	<0.0001
TMT-BA	132.70	76.68	80.31	46.57	−52.35	58.79	0.0002
RAVLT (immediate)	39.69	8.71	47.65	8.83	7.96	5.63	<0.0001
RAVLT (deferred)	8.38	2.99	10.42	2.76	2.04	1.99	<0.0001
CDT	6.98	1.71	8.50	1.25	1.52	1.75	0.0005
CPM	26.19	3.87	30.38	3.14	4.19	4.14	0.0001
FVC (L)	2.67	0.73	3.01	0.80	0.33	0.30	<0.0001
FEV_1 (L)	1.49	0.63	1.66	0.63	0.18	0.19	0.0002
FEV_1/FVC (%)	55.77	17.01	55.42	15.59	0.35	5.93	ns
SVC (L)	3.00	0.83	3.27	0.84	0.28	0.31	0.0001
IC (L)	2.02	0.76	2.38	0.69	0.37	0.49	<0.0001
6MWT (m)	345.60	138.50	438.30	106.60	92.77	62.16	<0.0001
BMI (kg/m^2)	27.46	6.29	26.52	6.02	−0.93	0.79	<0.0001
Fat mass (%)	27.38	8.07	26.44	7.53	−0.94	0.74	<0.0001
Steps/day	10,196	8,439	13,260	9,100	3,064	2,490	<0.0001
Energy expenditure (joules/3 days)	11,376.296	5,978.936	13,141.944	6,648.376	1,768,576.8	3,550,960.8	0.0007
Physical activity duration (minutes)	49.19	34.23	76.85	31.59	27.65	10.77	<0.0001
MRC	3.38	0.70	2.19	0.75	−1.19	0.49	<0.0001
BODE index	10.00	2.87	7.69	2.17	−2.31	1.44	<0.0001
CAT	19.96	3.65	15.46	3.40	−4.50	1.77	<0.0001

Abbreviations: 6MWT, 6-minute walk test; BMI, body mass index; BODE, BMI, obstruction, dyspnea, exercise capacity; CAT, COPD Assessment Test; CDT, Clock Drawing Test; CPM, Colored Progressive Matrices; FEV_1, forced expiratory volume in the 1st second; FVC, forced vital capacity; HADS-A, Hospital Anxiety and Depression Scale, anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale, depression subscale; HAM-D, Hamilton Depression Rating Scale; IC, inspiratory capacity; MRC, Medical Research Council; ns, nonsignificant; RAVLT, Rey Auditory Verbal Learning Test; SCL-90, Symptom Checklist 90; SD, standard deviation; STAI, State-Trait Anxiety Inventory; SVC, slow vital capacity; TMT, Trail Making Test.

Table 2 Descriptive and paired comparison analysis of psychometric and pneumological parameters at baseline and at 3 months in the depression-positive subgroup (n=38) and the depression-negative subgroup (n=14) of patients with COPD in a rehabilitation program

Parameters	Baseline		3 months		P-value
	Median	SD	Median	SD	
HAM-D					
Depressed	13.68	5.61	4.68	3.81	0.0000
Nondepressed	4.80	2.19	1.71	2.4	0.01
HADS-A					
Depressed	6.31	2.10	2.4	2.06	0.0000
Nondepressed	4.14	2.47	2.71	2.13	ns
HADS-D					
Depressed	9	4.24	3.42	2.755	0.0000
Nondepressed	5.85	1.21	2.57	1.90	0.01
STAI-1					
Depressed	41.89	10.20	31.21	6.42	0.0003
Nondepressed	37.57	3.15	28.57	4.99	0.007

(*Continued*)

Table 2 (*Continued*)

Parameters	Baseline		3 months		*P*-value
	Median	SD	Median	SD	
STAI-2					
Depressed	43.10	8.06	31.10	7.62	0.0000
Nondepressed	35.14	5.52	26.42	6.16	0.01
SCL-90					
Depressed	0.80	0.30	0.32	0.22	0.0000
Nondepressed	0.49	0.18	0.25	0.07	0.01
TMT-A					
Depressed	68	24.59	56.10	15.90	0.03
Nondepressed	67	16.11	50.14	10.23	0.05
TMT-B					
Depressed	202.36	87.74	139.15	51.25	0.0009
Nondepressed	195	68.25	114.42	44.22	0.01
TMT-BA					
Depressed	134.36	82.56	85.15	47.67	0.002
Nondepressed	128	63.36	67.14	44.02	0.02
RAVLT (immediate)					
Depressed	39.05	9.00	47.42	9.32	0.0000
Nondepressed	41.42	8.24	48.24	7.93	0.049
RAVLT (deferred)					
Depressed	8.63	2.81	10.57	2.83	0.0003
Nondepressed	7.71	3.59	10	2.7	0.04
CDT					
Depressed	7.13	1.57	8.73	1.17	0.0009
Nondepressed	6.57	2.14	7.85	1.31	ns
CPM					
Depressed	26.89	3.64	31.10	2.99	0.0001
Nondepressed	24.28	4.07	28.42	2.81	ns
FVC (L)					
Depressed	2.69	0.73	2.97	0.80	0.0003
Nondepressed	2.61	0.78	3.10	0.83	0.009
FEV$_1$ (L)					
Depressed	1.48	0.58	1.67	0.58	0.0009
Nondepressed	1.49	0.80	1.61	0.77	ns
FEV$_1$/FVC (%)					
Depressed	55.94	17.58	56.89	15.88	ns
Nondepressed	55.28	16.66	51.42	15.17	ns
SVC (L)					
Depressed	2.9	0.84	3.20	0.86	0.0008
Nondepressed	3.26	0.76	3.44	0.81	0.007
IC (L)					
Depressed	2.0	0.62	2.29	0.70	0.0006
Nondepressed	2.05	1.09	2.61	0.61	ns
6MWT (m)					
Depressed	326.57	144.75	421.15	110.9551	0.0000
Nondepressed	397.14	113.38	485	83.16	0.01
BMI (kg/m^2)					
Depressed	28.37	6.80	27.47	6.53	0.0001
Nondepressed	24.96	4.01	23.94	3.50	0.02
Fat mass (%)					
Depressed	28.59	8.76	27.59	8.11	0.0000
Nondepressed	24.08	4.9	23.31	4.84	0.02
Steps/day					
Depressed	8,646.63	5,887.314	11,351.21	7,306.701	0.0000
Nondepressed	14,401	12,825.98	18,442	11,915	0.02
Energy expenditure (kcal/3 days)					
Depressed	2,779.78	1,518.94	3,066.316	1,578.29	0.03
Nondepressed	2,553.286	1,242.21	3,345.42	1,726.28	ns

(*Continued*)

Table 2 (*Continued*)

Parameters	Baseline		3 months		*P*-value
	Median	**SD**	**Median**	**SD**	
Physical activity duration (minutes)					
Depressed	43.36	35.01	72.26	33.07	0.0000
Nondepressed	65	28.37	89	25.05	0.0000
MRC					
Depressed	3.4210	0.6924	2.2105	0.7873	0.0000
Nondepressed	3.28	0.75	2.14	0.69	0.004
BODE index					
Depressed	10.15	2.794	7.78	2.149	0.0000
Nondepressed	9.57	3.25	7.28	2.37	0.04
CAT					
Depressed	19.78	3.79	15.21	3.18	0.0000
Nondepressed	20.42	3.45	16.14	4.09	0.001

Abbreviations: 6MWT, 6-minute walk test; BMI, body mass index; BODE, BMI, obstruction, dyspnea, exercise capacity; CAT, COPD Assessment Test; CDT, Clock Drawing Test; CPM, Colored Progressive Matrices; FEV_1, forced expiratory volume in the 1st second; FVC, forced vital capacity; HADS-A, Hospital Anxiety and Depression Scale, anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale, depression subscale; HAM-D, Hamilton Depression Rating Scale; IC, inspiratory capacity; MRC, Medical Research Council; ns, nonsignificant; RAVLT, Rey Auditory Verbal Learning Test; SCL-90, Symptom Checklist 90; SD, standard deviation; STAI, State-Trait Anxiety Inventory; SVC, slow vital capacity; TMT, Trail Making Test.

(Table 3); the following parameters showed significant improvements:

- HAM-D (D subgroup: 9±2.19, ND subgroup: 3.14±6.20, *P*=0.02);
- HADS-A (D subgroup: 3.84±2.5, ND subgroup: 1:42±1.98, *P*=0.03); and
- SCL-90 (D subgroup: 0.486±0.287, ND subgroup: 0.247±0.177, *P*=0.05) (Table 3).

A significant correlation between psychometric (in particular, HADS-A, HADS-D, STAI-2, SCL-90, TMT-B, TMT-BA, and CPM) and internistic parameters was found, especially with fat mass and BMI in the total population: the reduction in fat mass and BMI was related to decreased anxiety and depression and improved QoL and cognitive performance (Tables 4 and 5; Figures 3–6).

At baseline in group D, a significant correlation was present between BMI and the following psychometric variables: HADS-A (*r*=0.47, *P*=0.04); HADS-D (*r*=0.5, *P*=0.02); SCL-90 (*r*=0.56, *P*=0.01); STAI-2 (*r*=0.51, *P*=0.02); TMT-A (*r*=0.52, *P*=0.02); TMT-B (*r*=0.44, *P*=0.05); RAVLT (*r*=−0.49, *P*=0.03); and CPM (*r*=−0.63, *P*=0.003) (Tables 4 and 5; Figures 5 and 6). These correlations were not statistically significant in subgroup ND.

A significant correlation between BMI and fat mass was present at baseline in subgroup D (*r*=0.8667, *P*=0.0000) but not in subgroup ND (*r*=0.3929, *P*=0.3833).

In subgroup D, the reduction in BMI was significantly related with fat mass (*r*=0.6072, *P*=0.005), but the same could not be affirmed for patients of the ND subgroup (Tables 4 and 5).

Discussion

In agreement with other findings,[5,6] we found a high prevalence (73%) of patients with depressive symptoms
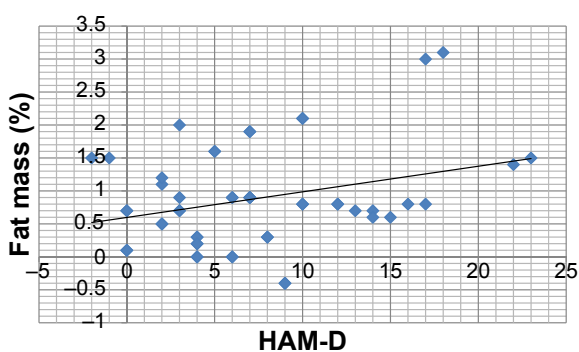

Figure 1 Scatterplot of absolute variations of HAM-D and fat mass from baseline to 3 months in the total sample of patients with COPD in a pulmonary rehabilitation program.
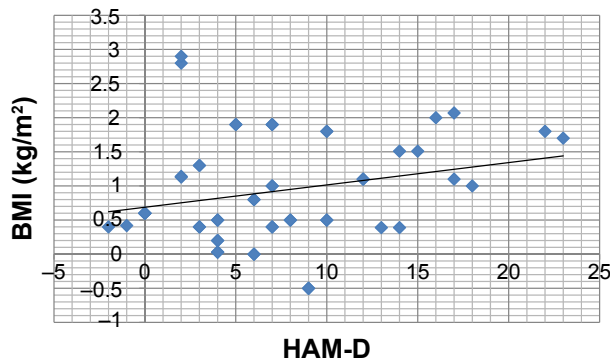**Abbreviation:** HAM-D, Hamilton Depression Rating Scale.

Figure 2 Scatterplot of absolute variations of HAM-D and BMI from baseline to 3 months in the total sample of patients with COPD in a pulmonary rehabilitation program.
Abbreviations: BMI, body mass index; HAM-D, Hamilton Depression Rating Scale.

Table 3 Unpaired comparison analysis of the differences following pulmonary rehabilitative treatment between the D and ND subgroups of patients with COPD

Comparison of variations between D and ND subgroups	Variation in subgroup D		Variation in subgroup ND		P-value
	Median	SD	Median	SD	
HAM-D	9	2.19	3.14	6.20	0.02
HADS-A	3.84	2.5	1.42	1.98	0.03
HADS-D	5.57	3.32	3.28	2.56	ns
STAI-1	10.6	10.33	9	5.94	ns
STAI-2	12	9.53	8.7	7.15	ns
SCL-90	0.486	0.287	0.247	0.177	0.05
TMT-A	11.89	22.52	16.85	18.32	ns
TMT-B	63.21	69.49	80.57	57.82	ns
TMT-BA	49.21	60.97	60.85	55.98	ns
RAVLT (immediate)	−8.36	5.02	−6.85	7.38	ns
RAVLT (deferred)	−1.94	1.89	−2.28	2.36	ns
CDT	−1.06	1.7	−1.28	1.82	ns
CPM	−4.21	3.72	−4.14	5.45	ns
FVC (L)	−0.28	0.27	−0.49	0.34	ns
FEV_1 (L)	−0.19	0.21	−0.11	0.13	ns
FEV_1/FVC (%)	−0.94	4.80	3.85	7.60	ns
SVC (L)	−0.30	0.33	−0.17	0.11	ns
IC (L)	−0.28	0.3	−0.56	0.82	ns
6MWT (m)	−94.57	63.25	−87.85	63.69	ns
BMI (kg/m^2)	0.9	0.74	1.02	0.93	ns
Fat mass (%)	1	0.76	0.77	0.68	ns
Steps/day	−286.5	533.09	−792.142	1,389.5	ns
Energy expenditure (kcal/3 days)	−108.52	75.23	−173	189.25	ns
Physical activity duration (minutes)	−28.89	12.09	−24.28	5.15	ns
MRC	1.21	0.41	1.14	0.69	ns
BODE index	2.36	1.11	2.14	2.19	ns
CAT	4.57	1.67	4.28	2.13	ns

Abbreviations: 6MWT, 6-minute walk test; BMI, body mass index; BODE, BMI, obstruction, dyspnea, exercise capacity; CAT, COPD Assessment Test; CDT, Clock Drawing Test; CPM, Colored Progressive Matrices; D, depression-positive; ND, depression-negative; FEV_1, forced expiratory volume in the 1st second; FVC, forced vital capacity; HADS-A, Hospital Anxiety and Depression Scale, anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale, depression subscale; HAM-D, Hamilton Depression Rating Scale; IC, inspiratory capacity; MRC, Medical Research Council; ns, nonsignificant; RAVLT, Rey Auditory Verbal Learning Test; SCL-90, Symptom Checklist 90; SD, standard deviation; STAI, State-Trait Anxiety Inventory; SVC, slow vital capacity; TMT, Trail Making Test.

at baseline in our COPD subjects that showed a significant decrease at the end of the rehabilitation program (7.7%). Previous reviews on pulmonary rehabilitation have indicated that 4-week programs can improve fatigue and emotional function, but these reviews included trials that did not specifically address effects on anxiety and depression,[36,46] while in our results, the mean HAM-D scores (used in our research to divide the whole population into the two subgroups and for the evaluation of the changes of depressive symptoms) decreased significantly both in the total sample and in the D and ND subgroups.

Another study examined the relationship between depression and aerobic exercise in generic chronic illness patients;[47] some others found a correlation between depression and/or anxiety and aerobic exercise in COPD patients undergoing pulmonary rehabilitation, but they did not investigate variables such as BMI or obesity.[36,48–51]

Moreover, in our trial, all other assessed psychiatric (depression, anxiety, and cognitive function) and medical/pneumological parameters demonstrated a significant improvement after the rehabilitation program.

The evaluation of cognitive performances, improved at 3 months, showed some peculiarities: the improvement in visual-spatial attention (TMT-A), although significant, was modest if compared with the TMT-B parameter, which assesses attention shifting ability and visual-spatial attention, as summarized by TMT-BA that represents the difference between the times of part B and those of part A in executive functioning (Table 1).

Memory, assessed by RAVLT, was significantly enhanced at 3 months both in immediate and in deferred recall (Table 1), such as praxic skills, mental representation, and planning (assessed by CDT) and deduction skills (evaluated through CPM) (Table 1).

Table 4 Correlation analysis of the difference in psychometric and pneumological parameters, observed at baseline and at 3 months in the subgroup (n=38) of depression-positive subjects with COPD in a pulmonary rehabilitation program

Depressed	FVC	FEV$_1$	FEV$_1$/FVC	SVC	IC	6MWT	BMI	Fat mass	Steps	Energy expenditure	Physical activity duration	MRC	BODE index	CAT
HAM-D	-0.0353	0.0569	0.4945*	-0.3181	-0.214	0.2468	0.4113	0.2713	0.1594	-0.2158	0.1659	0.3786	0.2703	0.1104
SCL-90	-0.753**	-0.3348	0.0238	-0.3477	0.1258	-0.1542	0.5616*	0.4598*	-0.122	-0.36	0.0321	0.224	0.1117	0.2063
STAI-I	-0.2131	-0.2611	-0.0885	-0.3058	-0.2962	-0.2179	0.3076	0.2833	-0.1398	-0.5919**	0.0035	0.3072	0.4801*	0.13
STAI-2	-0.1695	-0.3143	0.0509	-0.4099	-0.0379	-0.1689	0.5194*	0.5037*	0.0923	-0.3411	0.2026	0.189	-0.0059	0.074
HADS-A	-0.0085	0.2167	0.414	0.0124	-0.3571	0.0783	0.4738*	0.2515	0.0755	-0.3927	0.1117	0.2149	0.1031	0.1829
HADS-D	0.0191	0.0289	0.2886	-0.4364	0.0249	0.2671	0.5016*	0.3686	0.0692	-0.2456	0.3002	0.2978	0.2904	-0.1756
TMT-A	-0.0743	0.0418	0.1427	-0.4181	-0.183	0.0136	0.5209*	0.5097*	0.2388	-0.4004	0.1082	0	0.1343	-0.1821
TMT-B	-0.4848*	-0.267	-0.2789	-0.5897	-0.3842	0.0079	0.4466*	0.2504	-0.2439	-0.407	-0.1116	0.4714*	0.4905*	-0.066
TMT-BA	-0.3373	-0.2204	-0.2595	-0.3010	-0.4721*	0.0413	0.4316	0.2346	-0.4298	-0.1228	-0.2047	0.5185*	0.5209*	0.1577
RAVLT (immediate)	-0.1336	-0.2985	0.0556	0.3659	-0.2258	-0.3276	0.0544	-0.1212	0.0645	-0.1387	-0.3217	-0.1306	-0.1573	0.3226
RAVLT (deferred)	-0.08	-0.2266	-0.3731	-0.018	-0.243	-0.3712	-0.4963*	-0.3611	-0.0772	-0.0584	-0.0733	-0.0844	0.0802	-0.1018
CDT	0.4547	0.3038	0.3243	0.0035	-0.2236	0.2242	-0.1909	-0.1687	0.2284	0.1384	0.0446	-0.0829	-0.4341	-0.1631
CPM	0.3292	0.1923	0.0668	0.2284	0.0257	-0.0102	-0.6399*	-0.6184*	0.0619	0.1142	0.1086	-0.2021	0.1941	-0.1221

Notes: *Significant, $P<0.05$; **highly significant, $P<0.01$.
Abbreviations: BMI, body mass index; BODE, BMI, obstruction, dyspnea, exercise capacity; CAT, COPD Assessment Test; CDT, Clock Drawing Test; CPM, Colored Progressive Matrices; FEV$_1$, forced expiratory volume in the 1st second; FVC, forced vital capacity; HADS-A, Hospital Anxiety and Depression Scale, anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale, depression subscale; HAM-D, Hamilton Depression Rating Scale; IC, inspiratory capacity; MRC, Medical Research Council; RAVLT, Rey Auditory Verbal Learning Test; SCL-90, Symptom Checklist 90; STAI, State–Trait Anxiety Inventory; SVC, slow vital capacity; TMT, Trail Making Test; 6MWT, 6-minute walk test.
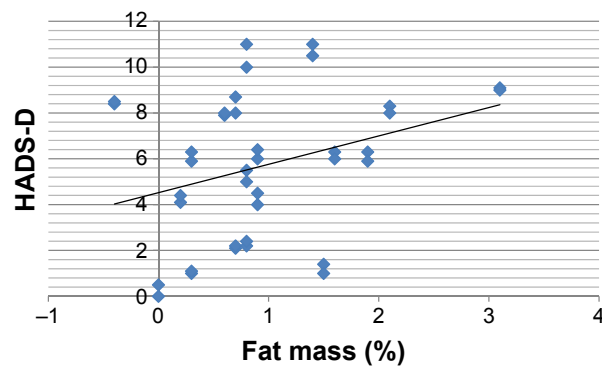
Table 5 Correlation analysis of the difference in psychometric and pneumological parameters, observed at baseline and at 3 months in the subgroup (n=14) of depression-negative subjects with COPD in a pulmonary rehabilitation program

Not depressed	FVC	FEV$_1$	FEV$_1$/FVC	SVC	IC	6MWT	BMI	Fat mass	Steps	Energy expenditure	Physical activity duration	MRC	BODE index	CAT
HAM-D	0.1836	0.2019	0.1468	-0.0918	0.5507	-0.0926	-0.3855	0.0367	0.569	-0.6792	-0.3855	-0.3788	-0.9446	-0.6741
SCL-90	-0.1261	-0.1622	0.1982	-0.0901	-0.1802	-0.4636	0.018	0.6667	-0.1622	-0.3964	-0.8829**	0.3618	-0.4091	-0.7006
STAI-I	-0.25	-0.0714	0.3571	-0.3571	-0.8571*	-0.2523	0.2143	0.7857	-0.6786	0.3571	-0.5357	0.7968*	0.3784	-0.3086
STAI-2	-0.2703	-0.0541	0.3424	-0.4144	-0.8289*	-0.3	0.1261	0.8108*	-0.6667	0.3964	-0.5225	0.804*	0.3545	-0.3114
HADS-A	-0.4491	-0.3181	0.5239	-0.2245	-0.2058	-0.3965	0.0936	0.5426	-0.3555	-0.4491	-0.7859*	0.3966	-0.2549	-0.8085*
HADS-D	-0.5455	-0.6547	-0.1091	0.046	0.0727	-0.5688	0.4183	0.5637	0.0727	0.1818	-0.1091	0.4564	-0.0826	0.1768
TMT-A	-0.4077	-0.5189	-0.0371	0.2224	0.593	-0.4862	-0.1482	-0.1112	0.0371	-0.7412	-0.4077	-0.2067	-0.4301	-0.4003
TMT-B	-0.4643	-0.8571*	-0.5	0.4643	0.25	-0.7027	0.5	0.3929	0.0714	0	-0.1786	0.3187	-0.036	0.3858
RAVLT (immediate)	0.2143	0.4643	0.3571	-0.3571	-0.8214*	0.3424	-0.0357	0.1786	-0.5714	0.3929	-0.1071	0.3386	0.5225	-0.1543
RAVLT (deferred)	0.3742	0.3555	0.1123	-0.0748	-0.8233*	0.2643	0.262	0.3555	-0.393	0.3555	-0.2433	0.3966	0.4059	-0.0202
CDT	0.0741	-0.2965	-0.1853	0.5189	-0.4077	0.2244	0.8524*	-0.0371	-0.2224	0.1853	0.1112	0.2067	0.561	0.524
CPM	0.7143	0.9643**	0.1071	-0.2857	0.2143	0.7568*	-0.6429	-0.6429	0.4643	0.0357	0.5357	-0.6773	-0.2342	-0.0386

Notes: *Significant, $P<0.05$; **highly significant, $P<0.01$.
Abbreviations: BMI, body mass index; BODE, BMI, obstruction, dyspnea, exercise capacity; CAT, COPD Assessment Test; CDT, Clock Drawing Test; CPM, Colored Progressive Matrices; FEV$_1$, forced expiratory volume in the 1st second; FVC, forced vital capacity; HADS-A, Hospital Anxiety and Depression Scale, anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale, depression subscale; HAM-D, Hamilton Depression Rating Scale; IC, inspiratory capacity; MRC, Medical Research Council; RAVLT, Rey Auditory Verbal Learning Test; SCL-90, Symptom Checklist 90; STAI, State–Trait Anxiety Inventory; SVC, slow vital capacity; TMT, Trail Making Test; 6MWT, 6-minute walk test.
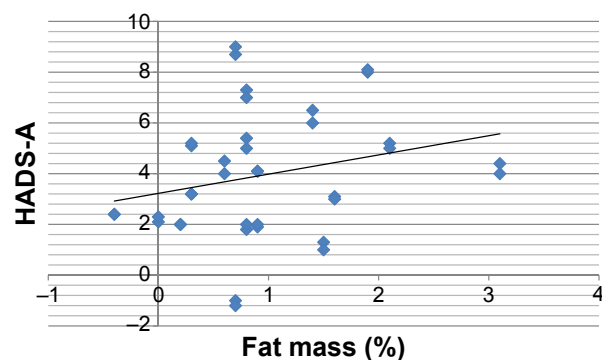
Figure 3 Scatterplot of absolute variations of fat mass and HADS-D from baseline to 3 months in the depression-positive subgroup of patients with COPD in a pulmonary rehabilitation program.
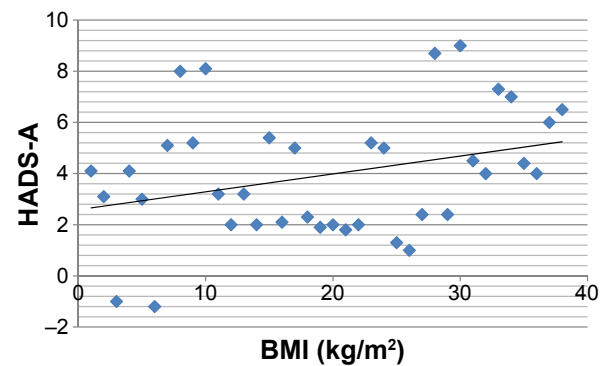**Abbreviation:** HADS-D, Hospital Anxiety and Depression Scale, depression subscale.

Figure 5 Scatterplot of absolute variations of BMI and HADS-A from baseline to 3 months in the depression-positive subgroup of patients with COPD in a pulmonary rehabilitation program.
Abbreviations: BMI, body mass index; HADS-A, Hospital Anxiety and Depression Scale, anxiety subscale.

We highlight the interesting correlations among STAI-1, MRC, and BODE (BMI, obstruction, dyspnea, exercise capacity) index: decrease in anxiety correlated with the improvement of dyspnea (MRC) and BODE index in the absence of correlation with objective indices such as forced expiratory volume in the 1st second, BMI, and 6MWT; this fact could be explained by the tendency of anxious depressed patients to amplify dyspnea.[52]

The improvement in psychological parameters (anxiety and depressive symptoms, QoL, and cognitive performances) was related to a general decrease of fat mass and BMI in the total sample (Tables 4 and 5). In subgroup D, this correlation was particularly evident between BMI and the following psychometric variables: HADS-A, HADS-D, SCL-90, STAI-2, TMT-A, TMT-B, RAVLT, and CPM (Table 4). Despite the general decrease of fat mass and BMI in the total sample, it was not statistically significant in subgroup ND, for which, unlike subgroup D (Table 5), there was no correlation between BMI and fat mass, both at baseline and

after the rehabilitation program. In this sense, BMI alone could be insufficient to explain the correlation with psychopathological parameters.

The different results observed between the two subgroups could be explained by the fact that D-subgroup patients presented a baseline condition of "overweight" and a higher fat mass percentage, not recorded in the ND subgroup, which was mainly composed of persons of normal weight. The only factor that indeed correlated with the majority of psychometric parameters was BMI, but only in subgroup D, where we recorded a correlation between BMI and fat mass.

In spite of the interesting findings, at least three limitations must be considered. First, metabolic and neurobiological analysis (eg, inflammatory and oxidative markers) could explain the link between anxiety and depressive symptoms and internistic medical disorders, such as COPD, in order to define a new meaning and management of them, but in this study was not performed. Second, the lack of
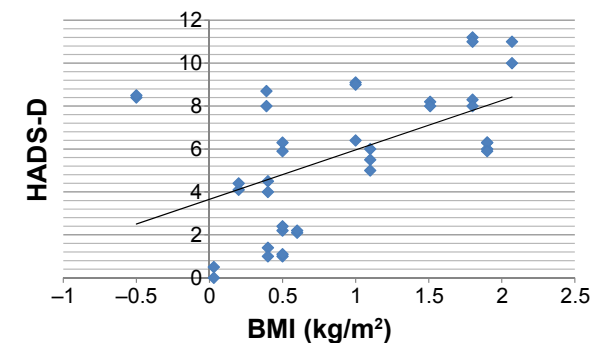

Figure 4 Scatterplot of absolute variations of fat mass and HADS-A from baseline to 3 months in the depression-positive subgroup of patients with COPD in a pulmonary rehabilitation program.
Abbreviation: HADS-A, Hospital Anxiety and Depression Scale, anxiety subscale.

Figure 6 Scatterplot of absolute variations of BMI and HADS-D from baseline to 3 months in the depression-positive subgroup of patients with COPD in a pulmonary rehabilitation program.
Abbreviations: BMI, body mass index; HADS-D, Hospital Anxiety and Depression Scale, depression subscale.

muscle mass evaluation could influence depressive and anxious symptoms.[53] Third, our sample size was small. So further studies are needed to evaluate the link between psychopathological symptoms and COPD in terms of inflammatory and oxidative markers with specific measures of them and the impact of muscle wasting on depression and anxiety in this specific population and, at the end, to augment the power of statistical analysis.

Conclusion

Our results suggest that it might be useful, in the context of multiple chronic diseases, to start a specific rehabilitation program (eg, of aerobic exercise) in order to establish a more appropriate and integrated therapeutic approach where there is suspicion, that needs to be confirmed, that a condition of increased adiposity could influence the genesis and evolution of psychiatric disorders.

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