

ORIGINAL RESEARCH

Relationship Between Depressive Symptoms and Hypogonadism in Men with COPD

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The prevalence of depression in chronic obstructive pulmonary disease (COPD) is greater than in the general population, but the mechanism is unknown. Depression has been linked mechanistically to testosterone deficiency, and testosterone deficiency (hypogonadism) affects many men with COPD. Accordingly, we hypothesized that significant depressive symptoms would be associated with hypogonadism in men with COPD. The hypothesis was tested in a prospective cross-sectional investigation of 104 men ($FEV_1 = 43 \pm 1\%$ predicted ($\pm SE$)), 36 of whom had significant depressive symptoms (Geriatric Depression Scale score or $GDS \geq 11$). Hypogonadism was present in 14 patients with $GDS \geq 11$ (39%) and in 21 with $GDS < 11$ (31%; $p = 0.41$). The independent association between depressive symptoms and gonadal state was evaluated after adjusting for potential confounders: combined severity of lung disease and functional impairment (BODE-index), co-morbidities (Charlson co-morbidity-index), age, active smoking, education, and marital status. After controlling for confounding variables, multivariable logistic-regression analysis revealed that only BODE-index (odds ratio 1.40; $p = 0.003$), lack of companion (2.73; $p = 0.045$) and younger age (0.93; $p = 0.021$) were independently associated with depressive symptoms. In a secondary analysis, patients were stratified into those with severe depressive symptoms ($GDS \geq 19$) and those with mild depressive symptoms ($GDS 11-18$). Prevalence of hypogonadism was greater in first group than in the second (62% vs. 26%; $p = 0.036$). After controlling for confounders, however, gonadal state was not associated with severe depressive symptoms. Similarly, gonadal state was not associated with mood and motivation subscale scores of the GDS. In conclusion, presence of significant depressive symptoms was not associated with hypogonadism in men with COPD.

Keywords: Chronic obstructive pulmonary disease, depression, hypogonadism, geriatric depression scale, BODE-index comorbidities, testosterone

INTRODUCTION

The risk of developing depressive symptoms is greater in patients with chronic obstructive pulmonary disease (COPD) than in the general population (1). In addition to personal suffering and mental anguish, depression in COPD is associated with more physical disability, greater difficulty in coping with the pulmonary disease, less success with smoking cessation, longer hospitalization during acute exacerbations and increased mortality (2,3).

Patients with COPD are exposed to a number of biophysiological, functional, social, and psychological processes that have been associated with increased risk of depression (4) – particularly in genetically-predisposed individuals (5). These include smoking, oxidative stress, vascular disease, decreased social contacts and physical and psychological stress (2).

Although not universally established (6;7), clinical (8–10) and laboratory (11) observations suggest that low testosterone levels may be an additional mechanism. Testosterone activates the serotonergic system in the frontal cortex, cingulate cortex and hippocampus (11,12). Testosterone also inhibits monoamine oxidase-A, the enzyme that catabolizes intraneuronal norepinephrine and serotonin in the medial prefrontal cortex (13) and decreases activity of the promoter for the corticotrophin-releasing hormone (14). These observations have direct implications for the hypothesized causal connection between low testosterone levels and depression.

First, all cortical areas listed above are important in the modulation of mood (15,16). Second, growing experimental evidence supports the role of low norepinephrine and serotonin levels in the pathogenesis of depression (4). Three, considerable evidence suggests that corticotrophin-releasing hormone and cortisol are involved in depression (4). The last three considerations raise the possibility that low testosterone levels (hypogonadism) could magnify the effect of biochemical, psychophysiological and social factors on the risk of developing depression (8). Considering the high prevalence of

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hypogonadism in men with COPD (17), and given the alleged mechanistic link between testosterone and depression (11,12), it would appear biologically plausible to predict a link between depressive symptoms and gonadal state in men with COPD.

In this study, the presence of depressive symptoms was determined using the Geriatric Depression Scale (GDS) (18–20). In addition to identifying patients with depressive symptoms, the GDS scale can also be used to stratify patients into those with mild and those with severe depressive symptoms (18). Furthermore, the GDS can be used to identify separate clusters of symptoms such as mood symptoms (mood subscale) and motivation symptoms (motivational subscale) (21).

The main objective of the study was to evaluate the relationship between hypogonadism and the presence of depressive symptoms in men with COPD. Specifically, we tested the primary hypothesis that hypogonadism would be associated with significant depressive symptoms in men with COPD. Two secondary analyses were also performed. One to explore the impact of the clinical characteristics (including gonadal state) on severity of depressive symptoms and another one to evaluate the impact of the clinical characteristics on mood and motivational subscale scores.

This is the first prospective cross-sectional investigation to directly explore the impact of gonadal state on depressive symptoms in men with COPD.

MATERIALS AND METHODS

Patients

One hundred and four men with COPD were enrolled. Patients were recruited from the outpatient clinic of the Division of Pulmonary and Critical Care Medicine of the Edward Hines, Jr. Hospital. Inclusion criteria were as follows: age 55 years or older, chronic airway obstruction (post-bronchodilator forced expiratory volume in one second of 70% predicted or less, ratio of forced expiratory volume in one second to forced vital capacity of 70% or less) (22), and stable clinical condition without an exacerbation during the preceding six weeks. Exclusion criteria included orchiectomy and current androgen and antiandrogen therapy. Patients with cirrhosis and alcoholism were excluded because these conditions can cause low testosterone concentrations. Appropriate institutional review board approved the study, and written consent was obtained.

Measurements

Demographic and clinical data. Demographic data were collected on enrolment in the study. Presence and severity of co-morbidities, including diagnosis of psychiatric disorders, were extracted from the patients' medical records and patient self-report (23).

Assessment of Depressive Symptoms. Presence of depressive symptoms was determined using the GDS developed by Yesavage et al (18). In contrast to other screening tools, such as the Hamilton Depression Rating Scale (24) and the Beck Depression Inventory (25), somatic complaints are ex-

cluded from the GDS items, as they are considered to reflect concerns that are part of the normal aging process. The GDS score ranges from 0 (no depression) to 30 (severe depression) (18;19).

In addition to the assessment of depressive symptoms in general, the GDS allows stratification of patients into those with mild depressive symptoms (GDS 11–18) and those with severe depressive symptoms (GDS \geq 19) (18). Furthermore, the GDS allows also the identification and quantification of separate clusters of symptoms such as mood symptoms (mood subscale) and motivation symptoms (motivational subscale) (21). The mood subscale, which consists of nine GDS items, reflects the presence of pessimistic outlook and sad mood. The motivational subscale consists of six items and identifies a loss of motivation or energy and difficulty in concentrating, making decisions, and problem solving (20;21).

BODE index. The multidimensional BODE index (26), as modified by Martinez et al. (27), was used to quantify the overall severity of lung disease and its impact on functional capacity. The four variables required for the calculation of the BODE index are: body mass index (B; kg/m²), degree of airflow obstruction (O; post-bronchodilator FEV₁ percent predicted), level of functional dyspnea (D; Shortness of Breath Questionnaire) (27) and exercise capacity (E; six-minute walking distance) (26). The BODE index can range from 0 (best functional capacity) to 10 (worse functional capacity) (26).

Charlson co-morbidity index. The Charlson co-morbidity index (28) was used to determine the impact of co-morbid conditions on depressive symptoms. The relative risk of each co-morbid condition is assigned integer weights which added can give a score ranging from 0 to 33, with higher scores indicating more comorbid conditions (28).

Pulmonary function tests. Lung volumes were measured by plethysmography and timed spirometry.

Blood samples. Morning blood samples were collected for measurement of free testosterone, total testosterone, and serum concentrations of luteinizing hormone. Free testosterone concentration was determined by equilibrium dialysis (Quest Diagnostics, Nichols Institute, San Juan Capistrano, CA). For this technique, the intra- and inter-assay coefficients of variation are 5.4 and 6.2% (29). Total testosterone concentration was determined by competitive immunoassay (Quest Diagnostics, Nichols Institute, San Juan Capistrano, CA) in the first 53 patients – both intra- and inter-assay coefficients of variation equal to 4.7% (29).

In the remaining 51 patients total testosterone concentration was determined by liquid chromatography tandem mass spectrometry (Quest Diagnostics, Nichols Institute, San Juan Capistrano, CA) – intra-assay coefficient of variation ranging from 9.1 to 10.8%, and inter-assay coefficient of variation ranging from 10.0 to 12.6% (30). Because total testosterone concentrations with these two techniques are equivalent (30), the concentrations of total testosterone obtained in the first group of patients were combined with concentrations of total testosterone measured in the second group of patients. Finally, two-site immunoassay was used to measure serum concentration of luteinizing hormone (Bayer Diagnostics,

Tarrytown, NY) – intra-assay and inter-assay coefficients of variation 2.9% and 2.4% (29).

Definition of hypogonadism. Hypogonadism was defined as the occurrence of free testosterone < 35 pg/ml for patients younger than 70 years, and free testosterone < 30 pg/ml for patients 70 years old and older (30). These thresholds have been identified by assessing free testosterone concentrations in 264 ambulatory healthy men between the ages of 18-89 years who were taking no medication (30).

Protocol

Eligible patients who agreed to take part in the study underwent pulmonary function testing, functional assessment (including 6-minute walking distance) (31), and collection of blood samples. Thereafter, patients completed the GDS (18) questionnaire and the Shortness of Breath Questionnaire (27). All patients were literate and none had any vision or manual dexterity impairment that restricted their ability to read and complete both self-administered (19,27) questionnaires without assistance. Patients were asked to complete the questionnaires independently (32).

Data analysis

The Kolmogorow-Smirnov test was used to assess distribution of data. Normally distributed data are presented as mean \pm standard error (SE). Non-normally distributed data are presented as median and interquartile ranges (IQR), and categorical variables are reported as proportions. Comparisons between patients experiencing significant depressive symptoms (GDS \geq 11) and patients without such symptoms (GDS < 11) were performed using unpaired Students t-test for normally distributed continuous variables, differences in median using Mann-Whitney U-test for skewed continuous variables and differences in frequencies using Pearson Chi-square, as appropriate.

Multivariable logistic regression analysis was performed to evaluate the impact of the clinical characteristics of patients on the presence of significant depressive symptoms (i.e., GDS \geq 11). The independent variables for the multivariable logistic regression analysis were: gonadal state, combined severity of lung disease and functional impairment (BODE index), active smoking, age, marital status (married/cohabitating), education (completed high school or above vs. less than high school), and Charlson co-morbidity-Index. Finally, 2 secondary analyses were also performed. In the first we explored the impact of the clinical characteristics (including gonadal state) in patients with severe depressive symptoms (GDS \geq 19) (18). In the second, we evaluated the impact of the clinical characteristics on mood and motivational subscale scores (21). Statistical analysis was performed using the Package for Social Sciences (version 18.0, SPSS, Chicago, IL). A value of $p < 0.05$ was considered significant.

Table 1. Characteristics of men with COPD who experienced significant depressive symptoms (Geriatric Depression Scale score \geq 11) and without such symptoms (*)

Variable	Significant depressive symptoms (GDS \geq 11)		P-value
	Present (n = 36)	Absent (n = 68)	
GDS, score	17 \pm 1	5 \pm 1	< 0.0001
Age, years	66 \pm 1	71 \pm 1	< 0.001
Hypogonadism, n (%)	14 (39%)	21 (31%)	0.411
Free-testosterone, pg/ml (IQR)	36 (27-61)	37 (29-51)	0.932
Total testosterone, ng/dl	362 (256-571)	332 (263-421)	0.315
Luteinizing hormone, mIU/ml	6 \pm 1	7 \pm 1	0.577
FEV ₁ , % predicted	42 \pm 3	44 \pm 2	0.421
BODE-index, median (IQR)	5 (3-7)	2.5(1 - 4)	0.001
Charlson's Co-morbidity-Index	2 (1-3)	2 (1-3)	0.969
Married/cohabitating, n (%)	15 (42%)	47 (69%)	0.007
Active smoking, n (%)	16 (44%)	17 (25%)	0.043
Completed high school or above, n (%)	12 (32%)	28 (41%)	0.434

(*) 8% of men who experienced significant depressive symptoms and 9% without such symptoms were African American. All the rest were Caucasians.

Definition of abbreviation: GDS = Geriatric Depression Scale; IQR = interquartile range; FEV₁ = forced expiratory flow in one second. Data are means \pm SE, median (interquartile range) and percentage.

RESULTS

Of 104 participants, 36 (35%) had significant depressive symptoms (GDS \geq 11) (Table 1). Twenty-one patients – 14 of 36 patients with GDS \geq 11 (39%) and 7 of 68 (10%) patients with a GDS < 11 – carried a diagnosis of mood disorder ($p = 0.029$). Of the 21 patients with mood disorder, one had a diagnosis of bipolar disorder and all the rest had a diagnosis of major depressive disorder. Of the 14 patients with a GDS \geq 11 and a diagnosis of mood disorder 9 were receiving medical treatment for depression. Of the 7 patients with a GDS < 11 and a diagnosis of depression, 3 were receiving medical treatment for depression.

Depressive symptoms and patients' characteristics

The prevalence of hypogonadism (30) was equivalent in patients with GDS scores in the depressed range and in patients with GDS scores below the depressed range (Table 1). BODE-index was worse in patients experiencing significant depressive symptoms than in patients without such symptoms (Table 1). More patients with high GDS were active smokers and were without a partner (no wife or a companion) than patients with low GDS (Table 1).

Of the four components of the BODE-index only the Shortness of Breath Questionnaire score was worse in patients with GDS \geq 11 than in patients with GDS < 11: 68 \pm 3 and 42 \pm 3 ($p < 0.0001$). In contrast, FEV₁ (42 \pm 3% and 44 \pm 2%, $p = 0.421$), body mass index (30 \pm 1 kg/m² and 29 \pm 1 kg/m²; $p = 0.552$) and six-minute walking distance

Table 2. Multivariable logistic analysis to determine relationship between significant depressive symptoms and patients' characteristics

Variable	Odd Ratio	95% CI	p-value
Hypogonadism	1.04	0.37 to 2.88	0.94
BODE-index	1.40	1.12 to 1.75	0.003
Lack of partner	2.73	1.02 to 7.30	0.045
Age	0.93	0.87 to 0.99	0.021
Active smoking	2.02	0.70 to 5.88	0.20
Charlson Co-morbidity-Index	0.93	0.63 to 1.37	0.70
Education (≥ 12 years)	0.83	0.30 to 2.26	0.71

(345 \pm 21 meters and 370 \pm 13 meters, $p = 0.276$) were equivalent in the two groups.

Variables associated with increased risk for depressive symptoms

Multivariable logistic-regression analysis showed that greater BODE-index (odds-ratio 1.40; $p = 0.003$), lack of partner (odds-ratio 2.73; $p = 0.045$) and younger age (odds-ratio 0.93; $p = 0.021$) were independently associated with depressive symptoms after controlling for gonadal state, active smoking, Charlson and level of education (Table 2).

Mood and motivational subscale scores

As expected, the motivational subscale score (that reflects cognitive complaints such as difficulty with problem-solving, decision-making and concentration) and the mood subscale scores (that reflects more sadness and pessimistic outlook) were higher in patients with GDS ≥ 11 (3.8 \pm 0.2 and 4.6 \pm 0.4) than in patients with GDS < 11 (2.5 \pm 0.1 and 0.6 \pm 0.1; $p < 0.00001$). On multivariable regression analysis, BODE-index, and younger age independently associated with GDS mood score ($p \leq 0.045$). In contrast, none of the seven independent variables were associated with motivational subscale score.

Subgroup analysis

Out of 36 patients with a GDS ≥ 11 , 23 patients had mild depressive symptoms (GDS 11-18) and 13 patients had severe depressive symptoms (GDS ≥ 19). In the sub-group with mild depressive symptoms the prevalence of hypogonadism was 26% and the corresponding value in the sub-group with severe depressive symptoms was 62% ($p = 0.036$). Despite the higher prevalence of hypogonadism in patients with severe depressive symptoms, on multivariable logistic-regression analysis gonadal state was not associated with severe depressive symptoms when controlling for BODE-index, partner, age, smoking, Charlson and level of education.

DISCUSSION

This is the first prospective cross-sectional study to directly explore the impact of hypogonadism on depressive symptoms (including mood and motivation) in men with COPD. The study has three major findings. First, testosterone defi-

ciency – when corrected for confounding factors – was not associated with a higher prevalence of significant depressive symptoms. Second, the overall severity of lung disease with its impact on functional capacity (BODE-index), lack of partner and younger age were independently associated with the occurrence of significant depressive symptoms. Lastly, BODE-index and younger age were also independently associated with the occurrence of pessimistic outlook and sad mood (mood subscale).

Impact of hypogonadism on depressive symptoms

Contrary to our hypothesis, testosterone deficiency – when corrected for confounding factors – was not associated with a higher prevalence of significant depressive symptoms. There are at least two possible explanations for this finding. First, the attributed risk of depressive symptoms secondary to low testosterone level is small-to-none. Second, testosterone affects mood only in a genetically-determined subgroup.

Our hypothesis that hypogonadism would be associated with significant depressive symptoms in men with COPD was based on published laboratory studies (11) and clinical observations conducted in patients who, for the most part, had no COPD (8,9). This association, however, has not been universally demonstrated (7) and it cannot be supported or refuted epidemiologically. This because it remains unclear whether prevalence of hypogonadism in men with COPD is greater than in the general population (17). (If low testosterone levels had a synergistic effect on depression in COPD a greater prevalence of hypogonadism paralleling the greater prevalence of depression in COPD would be expected.)

One way to reconcile our findings with studies supporting an association between low testosterone and depression (8,9,11) is the presence of genetic variability in the androgen-receptor gene (9,33). This gene has a highly polymorphic CAG trinucleotide repeat sequence, which results in a variable number of glutamines in the receptor's N-terminal (33). A shorter CAG-repeat length increases the gene's expression – i.e., increased transactivation (33). Results from the Massachusetts Male Aging Study (9) and the CARDIA Male Hormone study (33) suggest that the risk for depression is inversely proportional to the transactivation of the androgen receptor gene.

Non-testosterone factors and depressive symptoms

Factors (other than testosterone) that could play a role in determining depression in men with COPD include severity of lung disease, functional impairment, younger age, level of education, lack of companion, burden of co-morbidities, and smoking.

The possibility that severity of lung disease and greater functional impairment – as quantified by BODE-index – could predispose to depressive symptoms is supported by two findings. First, BODE-index was worse in patients experiencing depressive symptoms than in patients without such symptoms (Table 1). Second, BODE-index was independently associated with depressive symptoms (Table 2) (including mood subscale scores). The independent association between depressive symptoms and BODE-index is

supported by similar findings reported by Al-Shair et al. (34).

Lack of companion was strongly associated with significant depressive symptoms (Tables 1 and 2). This finding is in agreement with previous reports of lower rates of depression in married people or those cohabitating than in people who never married or who are divorced, separated or widowed (35,36). Whether lower rates of depression in married people result from social factors, selection bias, or a combination of both remains to be determined (37).

Patients with GDS ≥ 11 were younger than those with a GDS < 11 : 66 ± 1 years and 71 ± 1 years; $p < 0.001$ (Table 1). Younger age was also independently associated with a GDS ≥ 11 (Table 2). Cohort effect, healthy survivor bias, unwillingness to report symptoms and belief that depressed mood is part of the unavoidable aging process may all contribute to association between younger age and significant depressive symptoms (Table 2) (3,16,35).

All patients had a history of cigarette smoking, and more than 40% of those with depressive symptoms were active smokers (Table 1). Despite the higher prevalence of active smoking in patients with depressive symptoms (Table 1) and the reported association between smoking and depression (38;39) – particularly in men (40) – active smoking was not independently associated with significant depressive symptoms (Tables 2). In addition, active smoking did not discriminate between patients with and without sad mood or poor motivation. Several mechanisms could explain the absence of such associations. First, the relationship between smoking and depression is not causal but represents a common vulnerability to both smoking and depression (41). Second, history of smoking is sufficient to cause (irreversible) white matter damage (42). Such damage could in turn contribute to the development of depression (16).

Scores of Charlson co-morbidity-Index in patients with or without significant depressive symptoms were equivalent (Table 1). The equivalent burden of co-morbidities in the two groups is surprising considering that depression has been reported to be more prevalent in patients with medical co-morbidities than in those without medical co-morbidities (15). This finding raises the question of whether a unique synergism between COPD and perceived mood may be operative (43,44).

In persons younger than 54 years, lower socioeconomic status (less income, and low education) has been associated with increased prevalence of depression (45). In the current investigation, however, there was no association between level of education and significant depressive symptoms (Table 2). Older age and selection bias (most veterans receive care in the Veterans Administration system have low income) (46) may explain such discrepancy. This possibility is supported by an investigation of Borson et al. (47) who reported that neither level of education nor income distinguished between depressed and non depressed veterans 60 years old or older.

Treatment of depressive symptoms and depression

The 35% prevalence of significant depressive symptoms in the current investigation is in keeping with the 26 to 40% prevalence of depression in COPD reported in epidemiological studies (3,43). Nearly 60% of patients with GDS ≥ 11 carried no diagnosis of mood disorder. This result suggests an under-recognition of depressive symptoms and depression in patients with COPD – a frequent finding in investigations focused on depression in this patient population (3,48–50).

Of the 14 patients with a GDS ≥ 11 carrying a diagnosis of mood disorder, 9 (64%) were receiving medical treatment for depressive symptoms and depression. This finding raises two considerations. First, the high prevalence of patients receiving medical treatment for depressive symptoms and depression compares favorably to the 6-to-25% prevalence of patients receiving treatment for depressive symptoms reported by other investigators (3,48,49). Second, two-thirds of patients receiving medical treatment for depressive symptoms and depression had residual depressive symptoms. The prevalence of residual depressive symptoms has been reported to range between 32% (51) and 53% (52). Whether depressed men with COPD are at higher risk of experiencing residual symptoms of depression following initiation of antidepressants remains to be determined.

CRITIQUE OF METHODS

The relationship between COPD and depression is likely bidirectional (43). Depression that antedates COPD (early-onset depression) might serve as primary incentive to smoking (43) – tobacco smoking may attenuate depressive symptoms through nicotine-induced activation of dopaminergic, noradrenergic and serotonergic neural pathways and through compounds, other than nicotine, exerting potent inhibition of monoamine oxidase-A and B (38). Alternatively, in genetically susceptible individuals (5), the physical and psychological stresses accompanying COPD could increase the risk of depression (late-onset depression) (43). The cross-sectional design of the investigation does not allow grouping of patients between those with early-onset depression and those with late-onset depression. Such grouping could be relevant if onset of depression had an impact on depression-associated increased morbidity and mortality in COPD (2). To date, no such difference in outcome has been detected.

Testosterone levels can decrease during COPD exacerbations (53), and hospitalization due to COPD exacerbations are longer in patients who are depressed than in those who are not depressed (2,3). By study design, patients were studied when stable, therefore, any association between depression, COPD exacerbations and testosterone levels are beyond the scope of the current investigation.

Only men with COPD were enrolled in the current study. The limitation of enrolling only men is, however, tempered by recent observations of Schneider et al. (1). These investigators reported that risk of new-onset depression (and death after diagnosis of depression) in COPD tends to be higher in men than in women (1). Whether menopause and hormone

supplementation in women (10,54) with COPD could affect prevalence of mood disorders remains untested.

All patients in this study were veterans receiving care in a Veteran Administration hospital. The Veteran Administration patient population is known to have greater medical morbidity and socioeconomic stressors than a community based sample (55). The prevalence of significant depressive symptoms in our patients, however, was similar to the prevalence of significant depressive symptoms reported in studies where most (49) or all patients were not veterans (56,57). This observation suggests that our results may be applied to other populations of men with COPD.

Clinical implications

The role of testosterone supplementation for treatment of depression remains unclear (58). It has been suggested that testosterone supplements might be beneficial in men who exhibit low-to-borderline testosterone levels and a partial response to conventional antidepressants (58). The value of testosterone treatment in older men with COPD remains to be demonstrated (17). The issue is more than a theoretical concern: long-term testosterone supplementation can cause side effects, including increased risk of cardiovascular adverse events (59), polycythemia, sleep apnea, and prostatic hypertrophy (17).

Long-term effects of testosterone supplementation on risk of prostate cancer remains unknown (17). Our study was not intended to investigate whether testosterone replacement improves mood in men with COPD and low testosterone levels; nevertheless, our findings do not support use of such therapy if the goal is solely to lessen depressive symptoms. This finding complements our previous investigations (29,60) that could not support testosterone administration to hypogonadal men with COPD if the sole goal was to improve respiratory and limb muscle function, exercise capacity, respiratory symptoms or general health.

In summary, the mechanisms responsible for depression in COPD remain unclear. The cross-sectional data in this investigation do not support an association between depressive symptoms and low testosterone. In contrast, depressive symptoms were associated with severity of lung disease and COPD-associated functional impairment (BODE-index), lack of partner and younger age. The results in this investigation raise the additional possibility that combined severity of lung disease and functional impairment (BODE-index) and younger age heighten the risk for increased sadness and helplessness. In conclusion, in this prospective cross-sectional study, hypogonadism was not associated with significant depressive symptoms in men with COPD.

DECLARATION OF INTEREST

Declaration Of Interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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