RESEARCH ARTICLE

Associations of Vitamin D, chronic obstructive pulmonary disease and acute exacerbations of COPD with anxiety and depression: a nested case control study [version 1; peer review: awaiting peer review]

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Abstract

Background: Lower vitamin D levels have not only been associated with chronic obstructive pulmonary disease (COPD), exacerbations and lower lung functions, but also with anxiety and depression. We examined the associations of severity of anxiety and depression using HAM-A (Hamilton Anxiety Rating Scale) and HAM-D (Hamilton Depression Rating Scale) scores with COPD and vitamin D levels.

Methods: Observational nested case control study was conducted in MUDHRA cohort. One hundred COPD subjects and 100 age- gender-matched non-COPD subjects (controls) underwent evaluation of socioeconomic status, respiratory symptoms, spirometry, severity of anxiety and depression, six minute walk test and estimation of serum vitamin D levels. Independent association of low vitamin D levels with severity of anxiety and depression was assessed by logistic regression.
**Results:** COPD group had higher mean±SD anxiety and depression scores (HAM-A 8.0±3.5, HAM-D 8.72±4) compared to control group (HAM-A 4.51±2.2, HAM-D 4.3±2). The COPD group had 53 subjects with mild/moderate anxiety/depression whereas control group had 16 subjects with mild/moderate anxiety/depression. In COPD group, subjects with mild/moderate anxiety/depression had lower vitamin D levels compared to subjects with no/minimal anxiety/depression, while the difference in control group was not significant. In logistic regression, anxiety and depression levels had independent association with vitamin D levels, lung function variables, six-minute walk distance and presence of COPD. In COPD subgroup, anxiety and depression levels had independent association with breathlessness, GOLD FEV1 staging, CAT score, SGRQ-C Symptom score and exacerbation of COPD.

**Conclusions:** Greater proportion of COPD subjects suffer from anxiety and depression as compared to subjects without COPD. Severity of anxiety and depression was greater in COPD subjects. Poorer lung functions, higher respiratory symptoms and lower vitamin D levels are associated with higher levels of anxiety and depression in COPD subjects. There is an urgent need to recognise anxiety and depression in COPD patients.

**Keywords**
Anxiety, Depression, COPD, Vitamin D, Respiratory Symptoms, Acute exacerbation of COPD, HAM-A, HAM-D
Introduction
Globally, Chronic Obstructive Pulmonary Disease (COPD) is a well-recognised non-communicable disease (NCD) characterised by dyspnoea and near irreversible airflow limitation. COPD is the third leading cause of death globally, accounting for nearly million deaths in 2019 with over 80% of these in low-and middle-income countries1. According to the Global Burden of Diseases (GBD) Study 2017, the estimated prevalence of COPD is around 300 million1. In India during 2016, 8.7% of total deaths were caused by COPD1. A wide range of functional limitations and disabilities resulting from the effects of COPD is known to have an adverse impact on mental health. Comorbid depression and anxiety among persons with COPD is also known to compound disability, morbidity, and mortality and result in a higher burden to the health systems and society2–7.

It has been reported that patients with severe COPD are 2.5 times more likely to develop depression than those without COPD4. Earlier studies have been mostly inconclusive in relation to the causality of COPD and mental disorders, due to a range of factors related to study design, cohort size, duration of follow-up, measurements of depression and diagnostic criterion employed for diagnosis of COPD5. The relationship between COPD and mental health is complex, and emerging evidence indicates a possible bi-directional relationship with each of the conditions making the other worse. Psychological interventions like Cognitive Behavioural Therapy are known to alleviate depression and anxiety among those with COPD. Antidepressants and anxiolytics are known to aggravate symptoms of COPD and certain psychotropic medications may result in heightened stress levels, palpitations, and sleeping disorders along with a worsening of already existing COPD symptoms2,8,9.

Vitamin D and COPD, Vitamin D and anxiety and depression
Low levels of vitamin D has previously been associated with other NCDs like as osteoporosis, cancer, auto-immune diseases, and cardiovascular diseases10. A study demonstrated that supplementation of vitamin D may reduce the number of moderate to severe exacerbations of COPD11. There have also been indications that Vitamin D levels are negatively correlated with levels of anxiety and depression in persons with COPD12,13.

In this population based observational study, we examine the associations of vitamin D levels, COPD and its severity with HAM-A (Hamilton Anxiety Rating Scale) and HAM-D (Hamilton Depression Rating Scale) scores. We have evaluated the prevalence of anxiety and depression in those with COPD and examined a specific hypothesis that lower levels of vitamin D are associated with higher scores of anxiety and depression on the HAM-A and HAM-D scales respectively.

Methods
Ethical considerations
The study was approved by the Institutional Ethics Committee (IEC) at JSS Medical College, JSS Academy of Higher Education & Research (reference number JSS/MC/IEC/2519/2013-14, 31 July, 2014) and Institutional Review Board (IRB) of Florida International University (FIU), USA (IRB Protocol Approval #: IRB-14-0299, 16th October 2014). We only recruited those who provided full informed written consent.

Study design and population
In a well-established rural population-based cohort (Mysuru studies of Determinants of Health in Rural Adults cohort MUDIRA Cohort) we conducted a nested case control study in the district of Mysore, South India. The MUDIRA cohort profile has been previously published15. Between December 2014 – December 2015, 869 subjects from the original cohort were examined according to the Burden of Obstructed Lung Disease (BOLD) Study protocol12,13. Spirometry according to ATS/ERS (American Thoracic Society/European Respiratory Society) standards was performed and the diagnosis of COPD was made according to GOLD (Global Initiative for Obstructive Lung Diseases) criterion (age above 40 years, post bronchodilator FEV1/FVC ratio <0.70 in spirometry)12. Of the 869 examined, 108 subjects were diagnosed with COPD and 147 subjects had normal spirometry without any respiratory symptoms. With around 58.6% prevalence of vitamin D deficiency in rural adults, for margin error of 5% and confidence interval of 95%, minimum of 84 subjects are to be enrolled to the study. Of the 108 with COPD, we selected 100 ‘cases’ and a same number of age and gender matched ‘controls’ with normal spirometry (without COPD) by stratified random technique. The details about subject recruitment has been published previously16. The flow chart showing subject recruitment in this study is provided in extended data (Extended data: Supplemental Figure e1)

Data collection
All 200 participants (180 men and 20 women) underwent assessments to ascertain socio-economic positions by Standard of Living Index (SLI) questionnaire17, anxiety by Hamilton Anxiety Rating Scale (HAM-A)18, depression by Hamilton Depression Rating Scale (HAM-D)19, multi-morbidity by Charlson’s co-morbidity index20,21, and exercise capacity by a six-minute walk test22, according to standardised protocols by trained research assistants during house visits. Subjects who had habit of tobacco smoking during the time of the study were categorised as current smoker and subjects who had quit smoking for at least an year were categorised as ex-smokers23. Biomass fuel smoke exposure index was calculated by multiplying average hours of exposure to biomass fuel smoke per day with number of years of exposure24. The guidelines from Occupational Safety and Health Administration, USA was used to categorise occupational workload (physical activity level) as heavy work (heavy or very heavy levels) and non-heavy work (light or moderate levels)25. The severity of anxiety was graded as no/minimal anxiety (HAM-A ≤7), mild anxiety (HAM-A 8–17), moderate anxiety (HAM-A 18–24) and severe anxiety (HAM-A ≥25)26. Similarly, severity of depression was graded as no/minimal depression (HAM-D ≤7), mild depression (HAM-D 8–16), moderate depression (HAM-D 17–23) and severe depression (HAM-D ≥24)27.
The subjects with COPD had additional evaluation for respiratory symptoms with modified Medical Research Council (mMRC) dyspnoea grading, COPD Assessment Test (CAT Score)\(^\text{28}\) and St. George Respiratory Questionnaire-COPD (SGRQ-C)\(^\text{29}\). The COPD subjects were categorized on severity of airflow limitation in spirometry, and multi-dimensional assessment of COPD according to GOLD Guidelines\(^\text{30}\). Exacerbation of COPD was defined as a greater change in symptoms than the expected diurnal variation that would mandate additional clinical intervention such as prescription of additional medications (antibiotics or systemic steroids or both)\(^\text{30}\). Five mL of venous blood was drawn from all the participants to conduct vitamin D assay. Serum vitamin D (25-OH-Vitamin D) levels were estimated using the chemi-immuno-luminescence assay (CLIA) method [Elecsys Vitamin D total REF No. 05894913190, Roche, Basel, Switzerland]. The US Endocrine Society Guidelines defines Vitamin D levels of <20ng/ml as vitamin D deficiency\(^\text{32}\). All 200 (100 cases and 100 controls) subjects were revisited at 6 months, had repeat questionnaire administration, spirometry and assays for vitamin D levels\(^\text{33}\).

### Statistical analysis

The Epi info v7 (CDC, Atlanta, USA) and SPSS v20 (IBM Corp, Armonk, USA) software was employed for statistical analysis. Descriptive statistics included mean and standard deviation for continuous variables and frequencies for categorical/nominal variables. T-test was used for comparing differences in the means of continuously distributed variables between the group and Chi-square was used for comparing the differences in frequency/percentages of categorical variables between the groups. Pearson’s coefficients were derived to examine the correlations between HAM-A, HAM-D, vitamin D levels and other linear variables.

Linear regression analyses were carried to examine the associations of presence of COPD, FVC %Pred (post), FEV1 %Pred (Post), FEV1/FVC Ratio and Six Minute Walk Distance %Pred (independent variables) with the dependent continuous variables HAM-A and HAM-D scores. For dependent variables of logistic regression, HAM-A scores were converted into binary variable as no/minimal anxiety (scores ≤7) and mild/moderate (scores >7) anxiety. Similarly, HAM-D scores were converted as no/minimal depression (scores ≤7) and mild/moderate depression (scores >7). The regression analyses were also conducted in the COPD sub-group for which the independent variables were presence of breathlessness, mMRC breathlessness grade, Global Initiative for Obstructive Lung Diseases (GOLD) FEV1 staging, COPD Assessment Test (CAT) score, St. George Respiratory Questionnaire-COPD (SGRQ-C) scores (SGRQ-C Total, SGRQ-C Symptom, SGRQ-C Activity, SGRQ-C Impact), history of COPD exacerbations and number of exacerbations. The regression models were adjusted for age, Body Mass Index (BMI), Charlson’s Co-morbidity Index Score (CCI Score), Standard of living Index (SLI), smoking pack years and vitamin D levels. P-value of <0.05 was considered statistically significant.

### Results

Demographic and clinical characteristics of the 200 participants are provided in Table 1. The majority of the participants were engaged in occupations that involved heavy work. Charlson’s comorbidity score was low among all subjects. Standard of Living Index score between the cases and controls was similar and most of them belonged to medium socioeconomic status. HAM-A score had a range of 1–20 (mean±SD of 6.26±3.4) and the range for HAM-D score was 1–23 (mean±SD of 6.52±3.86). Here, 154 subjects had no/minimal anxiety, 38 subjects had mild and 8 subjects had moderate anxiety. Similarly, 147 subjects had no/minimal depression, 46 had mild and 7 subjects had moderate depression. None of the subjects had severe anxiety or severe depression.

The mean±SD HAM-A score in control group was 4.51±2.2, was much lower than in the COPD group (8.0±3.5, p-value <0.001). Similarly, the mean±SD HAM-D score was 4.3±2 in control group and much lower than in the COPD group (8.72±4; p<0.001). In the control group, 84 subjects had no/minimal anxiety or depression; whereas in COPD group, 53 patients had mild/moderate anxiety or depression. The Table 2 compares select variables between No/Minimal anxiety or depression and mild/Moderate anxiety or depression for non-COPD and COPD groups separately. As expected, mean smoking pack years was much higher among those with COPD than controls irrespective of severity of anxiety and depression scores.

In the COPD group, a significant difference in mean vitamin D levels was observed between the subjects of no/minimal anxiety or depression, compared to mild/moderate anxiety or depression (p-value <0.001); while in the control group, this difference was not significant (p-value 0.99). Among COPD subjects, there was a significant difference between the mean values of Body Mass Index (p=0.043), Six Minute Walk Distance (SMWD) (p<0.0001) and Spirometry variables (post bronchodilator), FVC %predicted, FEV1 %predicted and FEV1/FVC Ratio (p<0.0001, <0.0001 and 0.029, respectively) of those with anxiety or depression and those without.

The scatterplots (Figure 1 and Figure 2) show the relation between selected variables and the HAM-A & HAM-D scores of subjects. Spirometry parameters, SMWD and vitamin D levels are inversely correlated with anxiety and depression scores among COPD subjects only, but not among the controls. The correlation coefficients and p-values are given in Extended data (Supplemental Tables e1a and e1b\(^\text{54}\)). The box plots (Figure 3a-d) illustrate the HAM-A and HAM-D scores among the subjects with COPD. Here the GOLD stage 4 or those having 3 or more exacerbations, and D group of ABCD grouping of COPD have a higher HAM-A and HAM-D score. Similarly, with respect to breathlessness, subjects with a higher mMRC grade scores show higher HAM-A and HAM-D scores.

In the multiple linear regression models, the vitamin D levels, lung function variables, six-minute walk distance and presence of COPD had independent association with HAM-A and HAM-D scores. For every unit decrease in vitamin D level, the HAM-A and HAM-D scores increases by 0.16 (p<0.001) and 0.20 (p<0.001), respectively. The subjects with COPD had 3.5 (p<0.001) and 4.4 (p<0.001) units higher score of HAM-A and HAM-D, respectively, compared to those without...
Table 1. Demographic characteristics and anxiety depression severity scores among COPD and healthy study participants in Mysore, India.

| Variables                  | All subjects | Anxiety severity (HAM-A Score) | Depression severity (HAM-D Score) |
|----------------------------|--------------|-------------------------------|----------------------------------|
|                            | n=200        | ≤7                            | 8-17                             | >18                              | ≤7          | 8-16       | ≥17        | P-value |
|                            |              | No/minimal n(%)               | Mild n(%)                        | Moderate n(%)                    | No/minimal n(%) | Mild n(%) | Moderate n(%) |        |
| COPD status                |              |                               |                                 |                                  |              |            |            |        |
| Non-COPD                  | 100          | 92 (92)                        | 8 (8)                            | 0 (0)                            | 91 (91)       | 9 (9)      | 0 (0)      | 0.000   |
| COPD                      | 100          | 62 (62)                        | 30 (30)                          | 8 (8)                            | 56 (56)       | 37 (37)    | 7 (7)      | 0.000   |
| Age in years              |              |                               |                                 |                                  |              |            |            |        |
| Mean±SD                   | 57.36±10.0   | 57.0±9.6                       | 57.8±11.2                        | 61.9±12.8                       | 57.5±9.6      | 56.5±10.8 | 59.3±14.8 | 0.72    |
| ≤45                       | 36           | 27 (75)                        | 8 (22.2)                         | 1 (2.8)                         | 25 (69.4)     | 9 (25)     | 2 (5.6)   | 0.2     |
| 46-55                     | 55           | 41 (74.6)                      | 12 (21.8)                        | 2 (3.6)                         | 37 (67.3)     | 17 (30.9)  | 1 (1.8)   |         |
| 56-65                     | 71           | 62 (87.3)                      | 7 (9.9)                          | 2 (2.8)                         | 59 (83.1)     | 11 (15.5)  | 1 (1.4)   |         |
| >65                       | 38           | 24 (63.1)                      | 11 (29)                          | 3 (7.9)                         | 26 (68.4)     | 9 (23.7)   | 3 (7.9)   |         |
| Gender                    |              |                               |                                 |                                  |              |            |            |        |
| Females                   | 20 (10)      | 15 (75)                        | 3 (15)                           | 2 (10)                          | 15 (75)       | 5 (25)     | 0 (0)      | 0.000   |
| Males                     | 180 (90)     | 139 (77.2)                     | 35 (19.5)                        | 6 (3.3)                         | 132 (73.3)    | 41 (22.8)  | 7 (3.9)   | 0.67    |
| Smoking habits (males)    |              |                               |                                 |                                  |              |            |            |        |
| Never smoker              | 15 (8.33)    | 14 (93.3)                      | 1 (6.7)                          | 0 (0)                           | 13 (86.7)     | 2 (13.3)   | 0 (0)      |         |
| Ever smoker               | 165 (91.67)  | 125 (75.8)                     | 34 (20.6)                        | 6 (3.6)                         | 119 (72.1)    | 39 (23.6)  | 7 (4.2)   | 0.44    |
| Ex-smoker                 | 51 (30.9)    | 39 (76.5)                      | 11 (21.6)                        | 1 (1.9)                         | 36 (70.6)     | 12 (23.5)  | 3 (5.9)   |         |
| Current smoker            | 114 (69.1)   | 86 (75.4)                      | 23 (20.2)                        | 5 (4.4)                         | 83 (72.8)     | 27 (23.7)  | 4 (3.5)   | 0.7     |
| Occupation                |              |                               |                                 |                                  |              |            |            |        |
| Heavy work                | 166 (83)     | 128 (77.1)                     | 34 (20.5)                        | 4 (2.4)                         | 123 (74.1)    | 38 (22.9)  | 5 (3)     |         |
| Non-heavy                 | 34 (17)      | 26 (76.4)                      | 4 (11.8)                         | 4 (11.8)                        | 24 (70.6)     | 8 (23.5)   | 2 (5.9)   | 0.7     |
| Education                 |              |                               |                                 |                                  |              |            |            |        |
| Illiterate                | 7            | 6 (85.7)                       | 1 (14.3)                         | 0 (0)                           | 6 (85.7)      | 1 (14.3)   | 0 (0)     |         |
| Primary school            | 184          | 141 (76.6)                     | 35 (19)                          | 8 (4.4)                         | 134 (72.8)    | 43 (23.4)  | 7 (3.8)   |         |
| High school               | 8            | 6 (75)                         | 2 (25)                           | 0 (0)                           | 6 (75)        | 2 (25)     | 0 (0)     |         |
| Degree                    | 1            | 1 (100)                        | 0 (0)                            | 0 (0)                           | 1 (100)       | 0 (0)      | 0 (0)     | 0.97    |
| CCI score                 |              |                               |                                 |                                  |              |            |            |        |
| Mean±SD                   | 1.41±1.1     | 1.37±1.1                       | 1.47±1.2                         | 1.75±1.3                        | 0.59#         | 1.43±1.1   | 1.3±1.2    | 1.57±1.5 | 0.73#   |
| 0-1                       | 104 (52)     | 82 (78.9)                      | 19 (18.3)                        | 3 (2.8)                         | 73 (70.2)     | 28 (26.9)  | 3 (2.9)   |         |
| 2-4                       | 96 (48)      | 72 (75)                        | 19 (19.8)                        | 5 (5.2)                         | 74 (77.1)     | 18 (18.8)  | 4 (4.1)   | 0.37    |
| Standard of living index (SLI) | 19.46±2.8   | 19.3±2.9                       | 20.2±2.3                         | 19.8±3.2                        | 0.2           | 19.4±2.8   | 19.7±2.9   | 19±2.7   | 0.71    |
| ≥20                       | 99 (49.5)    | 72 (72.7)                      | 23 (23.3)                        | 4 (4)                           | 71 (71.7)     | 25 (25.3)  | 3 (3)     |         |
| <20                       | 101 (50.5)   | 82 (81.2)                      | 15 (14.8)                        | 4 (4)                           | 76 (75.2)     | 21 (20.8)  | 4 (4)     | 0.73    |
| Variables                          | All subjects | Anxiety severity (HAM-A Score) | Depression severity (HAM-D Score) | P-value |
|-----------------------------------|--------------|-------------------------------|----------------------------------|---------|
|                                   | n=200        | ≤7                            | 8-17                            | >18     | ≤7 | 8-16 | ≥17 |         |
|                                   | N=154        | 20.9±2.9                      | 21.2±3.1                        | 19.9±2.6 | 20.9±2.7 | 21.2±3.4 | 18.8±2.2 | 0.12   |
|                                   | N=38         | 21.5±2.9                      | 20.9±3.1                        | 1 (2.4)  | 29 (67.4) | 11 (25.6) | 3 (7)   |         |
|                                   | N=8          | 21.3±3.2                      | 17 (6.1)                        | 89 (78.1)| 21 (18.4) | 4 (3.5)   |         |         |
|                                   | N=147        | 20.9±2.7                      | 21.2±3.4                        | 18.8±2.2 | 0.12   |         |         |         |
|                                   | N=46         | 20.9±2.7                      | 21.2±3.4                        | 18.8±2.2 | 0.12   |         |         |         |
|                                   | N=7          | 20.9±2.7                      | 21.2±3.4                        | 18.8±2.2 | 0.12   |         |         |         |
| Body Mass Index (BMI)             |              |                               |                                  |         |         |         |         |         |
| Mean±SD                           | 20.88±2.9    | 20.9±2.9                      | 21.2±3.1                        | 19.9±2.6 | 20.9±2.7 | 21.2±3.4 | 18.8±2.2 | 0.12   |
| <18.5 (underweight)               | 43 (21.5)    | 33 (76.7)                      | 9 (20.9)                        | 1 (2.4)  | 29 (67.4) | 11 (25.6) | 3 (7)   |         |
| 18.5-22.9 (normal)                | 114 (57)     | 90 (79)                        | 17 (14.9)                       | 7 (6.1)  | 89 (78.1) | 21 (18.4) | 4 (3.5) |         |
| 23-24.9 (overweight)              | 31 (15.5)    | 22 (71)                        | 9 (29)                          | 0 (0)    | 23 (74.2) | 8 (25.8) | 0 (0)   |         |
| 25-30 (pre-obese)                 | 12 (6)       | 9 (75)                         | 3 (25)                          | 0 (0)    | 6 (50)    | 6 (50)   | 0 (0)   | 0.15   |
| Vitamin D levels (ng/mL)          |              |                               |                                  |         |         |         |         |         |
| Mean±SD                           | 18.25±5.6    | 19.6±5                         | 14.2±5.4                        | 12.4±5.1 | 0.000   | 19.6±4.8 | 15.7±5.5 | 6.8±2   | 0.000   |
| >20                               | 71 (35.5)    | 66 (93)                        | 5 (7)                           | 0 (0)    | 62 (87.3) | 9 (12.7) | 0 (0)   |         |
| ≤20 (deficiency)                  | 129 (64.5)   | 88 (68.2)                      | 33 (25.6)                       | 8 (6.2)  | 0.000   | 85 (65.9) | 37 (28.7) | 7 (5.4) | 0.003   |
| Six minute walk distance (% predicted) |          |                               |                                  |         |         |         |         |         |
| Mean±SD                           | 68.04±16.1   | 72.1±14.2                      | 55.2±15.9                       | 51.3±7   | 0.000   | 72.5±14.3 | 56.7±14.9 | 47.7±7.7 | 0.000   |
| ≥ 80%                             | 59 (29.5)    | 55 (93.2)                      | 4 (6.8)                         | 0 (0)    | 56 (94.9) | 3 (5.1) | 0 (0)   |         |
| < 80                              | 141 (70.5)   | 99 (70.2)                      | 34 (24.1)                       | 8 (5.7)  | 0.002   | 91 (64.5) | 43 (30.5) | 7 (5)   | 0.000   |
| Spirometry post bronchodilator (Mean±SD) |          |                               |                                  |         |         |         |         |         |
| FVC % predicted                   | 76.52±19.3   | 81.0±16.8                      | 63.7±19.9                       | 50.5±11.6| 0.000   | 81.8±16.1 | 62.4±20.3 | 57.9±16.9 | 0.000   |
| FEV1 % predicted                  | 71.79±25.6   | 74.3±9.1                       | 65.2±12.2                       | 54.6±4.4 | 0.000   | 74.9±8.9  | 64.3±11.1 | 56.3±11.5 | 0.000   |
| FEV1/FVC                          | 71.79±10.9   | 78.2±22.5                      | 53.8±25                         | 34.1±8.6 | 0.000   | 79.4±21.7 | 52.2±24.9 | 40.1±13.8 | 0.000   |
| COPD subjects:                    |              |                               |                                  |         |         |         |         |         |
| GOLD FEV1 Staging                 |              |                               |                                  |         |         |         |         |         |
| Mild                              | 5            | 5 (100)                        | 0 (0)                           | 0 (0)    | 4 (80)   | 1 (20)   | 0 (0)   |         |
| Moderate                          | 40           | 27 (67.5)                      | 13 (32.5)                       | 0 (0)    | 29 (72.5) | 9 (22.5) | 2 (5)   |         |
| Severe                            | 40           | 27 (67.5)                      | 8 (20)                          | 5 (12.5) | 20 (50)  | 17 (42.5) | 3 (7.5) |         |
| Very Severe                       | 15           | 3 (20)                         | 9 (60)                          | 3 (20)   | 0.000   | 3 (20)   | 10 (66.7) | 2 (13.3) | 0.000   |
| SGRQ-C Score (Mean±SD)            |              |                               |                                  |         |         |         |         |         |
| SGRQ-C Total                      | 35.1±5.1     | 34.7±5.3                       | 35.4±7.1                        | 38.5±6.7 | 0.014   | 34.9±4.9 | 35.3±5.6 | 35.6±5.5 | 0.9     |
| SGRQ-C Symptom                    | 56.1         | 53.6±18.9                      | 58.7±11.3                       | 65.4±10  | 0.007   | 52.8±10.8 | 59.8±11.6 | 62.4±7.6 | 0.004   |
| SGRQ-C Impact                     | 27.8±7       | 28±6.7                         | 27.6±7.5                        | 27.4±8   | 0.95    | 28.6±6.8 | 27.2±7   | 25.7±8.9 | 0.5     |
| SGRQ-C Activity                   | 35.2±9       | 35±9.2                         | 33.9±8.4                        | 42±5.3   | 0.07    | 35.2±9   | 35±9.4  | 36.7±6.7 | 0.9     |
### Variables

| All subjects | Anxiety severity (HAM-A Score) | Depression severity (HAM-D Score) |
|--------------|-------------------------------|-----------------------------------|
|              | ≤7  | 8-17 | >18 | ≤7  | 8-16 | ≥17   |
| n=200        | N=154 | N=38 | N=8 | N=147 | N=46 | N=7   |

#### CAT Score

| CAT Score | n=200 | No/minimal n(%), Mild n(%), Moderate n(%) | P-value | No/minimal n(%), Mild n(%), Moderate n(%) | P-value |
|-----------|-------|-------------------------------------------|---------|-------------------------------------------|---------|
| Mean±SD   | 17.9±5.6 | 16.6±5.2, 18.9±5.5, 24.8±2.2 | 0.000 | 16.5±5.4, 19.3±5.3, 22±5.7 | 0.008 |

#### mMRC Breathlessness Grade

| mMRC Breathlessness Grade | Median | Grade 0 | Grade 1 | Grade 2 | Grade 3 |
|---------------------------|--------|---------|---------|---------|---------|
| Mean±SD                  | 0.8±0.82 | 0.44±0.7, 1.4±0.7, 1.5±0.5 | 0.4±0.6, 1.2±0.8, 1.7±0.8 | 0.000# |
| Grade 0                  | 41     | 40 (97.6), 1 (2.4), 0 (0) | 36 (87.8), 5 (12.2) | 0 (0) |
| Grade 1                  | 42     | 18 (42.9), 20 (47.6), 4 (9.5) | 18 (42.9), 21 (50), 3 (7.1) | 0 (0) |
| Grade 2                  | 13     | 3 (23.1), 6 (46.1), 4 (30.8) | 1 (7.7), 9 (69.2), 3 (23.1) | 0 (0) |
| Grade 3                  | 4      | 1 (25), 3 (75), 0 (0) | 1 (25), 2 (50), 1 (25) | 0.000 |

#### COPD Exacerbations

| COPD Exacerbations | 0 | 1 | 2 | ≥3 |
|--------------------|---|---|---|----|
| 0                  | 58 | 49 (84.5), 9 (15.5), 0 (0) | 46 (79.3), 12 (20.7) | 0 (0) |
| 1                  | 19 | 13 (68.4), 5 (26.3), 1 (5.3) | 8 (42.1), 11 (57.9) | 0 (0) |
| 2                  | 18 | 0 (0), 14 (77.8), 4 (22.2) | 2 (11.1), 13 (72.2) | 3 (16.7) |
| ≥3                 | 5  | 0 (0), 2 (40), 3 (60) | 0.000 | 0 (0), 1 (20), 4 (80) | 0.000 |

#### ABCD Group of COPD

| ABCD Group of COPD | A | B | C | D |
|--------------------|---|---|---|---|
|                   | 10| 82| 0| 8 |
|                   | 8(80), (20), (0) | 23(28), 5(6.1) | 0(0), 0(0), 0(0) | 5(62.5), 3(37.5), 0.001 |
|                   | 7(70), 3(30), 0(0) | 47(57.3), 33(40.2), 2(2.5) | 0(0), 0(0), 0(0) | 2(25), 1(12.5), 5(62.5) |

Values expressed as frequency(percentage) p-values by chi-square test; Mean±SD p-values by T-test. # Non-parametric test.

Occupational workload categories Heavy work (heavy or very heavy levels) and Non-heavy work (light or moderate levels) are based on workloads (physical activity level) from Occupational Safety and Health Administration, USA.

Education categories based on years of formal education. Primary school: literate or less than 10 years; High school: completed 10 years; Degree: 15 years of formal education.

GOLD: Global Initiative for Obstructive Lung Disease; SGRQ-C: St George’s Respiratory Questionnaire- COPD; CAT: COPD Assessment Test; mMRC: Modified Medical Research Council; ABCD Group: Multi-dimensional assessment of COPD according to GOLD guidelines. CCI: Charlson’s Comorbidity Index. HAM-A: Hamilton Anxiety Rating Scale. HAM-D: Hamilton Depression Rating Scale. FVC: Forced vital capacity. FEV1: Forced expiratory volume in 1st second.

COPD. The regression coefficients for the different models of linear regression with lung function variables and six-minute walk test are shown in Table 3a. Sub-group analysis in COPD group showed that for every unit decrease in vitamin D level, the HAM-A and HAM-D scores increased by 0.01 (p<0.001) and 0.16 (p<0.001) units respectively. The subjects with a history of exacerbation of COPD had 3.8 (p<0.001) and 4.2 (p<0.001) higher units of HAM-A and HAM-D respectively compared to the COPD subjects without exacerbations. For each exacerbation, the HAM-A score increased by 2.3 (p<0.001) units and HAM-D score increased by 2.6 (p<0.001) units. The regression coefficients for the different models of linear regression among COPD subjects with respiratory symptoms, and GOLD staging of airflow limitation are given in Table 3b.
Table 2. Comparison of select variables between No/Minimal, Mild/Moderate anxiety or depression, among the Non-COPD and COPD groups in Mysore, India.

| Variables                     | Non-COPD (n=100) | COPD (n=100) |
|-------------------------------|------------------|--------------|
|                               | Anxiety or depression | P-value | Anxiety or depression | P-value |
|                               | No/Minimal (n=84) | Mild/Moderate (n=16) | No/Minimal (n=47) | Mild/Moderate (n=53) |
| Age in years                  |                  |              |                  |              |
| Mean±SD                       | 57.2±9.9         | 55.25±8.2    | 0.4              | 58.02±8.9    | 57.6±11.7    | 0.7      |
| ≤45                           | 16 (88.9)        | 2 (11.1)     | ref              | 6 (33.3)     | 12 (66.7)    | ref      |
| 46–55                         | 19 (70.4)        | 8 (29.6)     | 0.3              | 12 (44.4)    | 15 (56.6)    | 0.7      |
| 56–65                         | 32 (88.9)        | 4 (11.1)     | 1                | 24 (66.7)    | 12 (33.3)    | 0.03     |
| >65                           | 17 (89.5)        | 2 (10.5)     | 1                | 5 (26.3)     | 14 (73.7)    | 0.6      |
| Gender                        |                  |              |                  |              |
| Females                       | 9 (90)           | 1 (10)       | ref              | 5 (50)       | 5 (50)       | ref      |
| Males                         | 75 (83.3)        | 15 (16.7)    | 1                | 42 (46.7)    | 48 (53.3)    | 1        |
| Smoking habits (180 males)    |                  |              |                  |              |
| Never smoker                  | 10 (83.3)        | 2 (16.7)     | ref              | 2 (66.7)     | 1 (33.3)     | ref      |
| Ever smoker                   | 65 (83.3)        | 13 (16.7)    | 1                | 40 (46)      | 47 (54)      | 0.9      |
| Ex-smoker                     | 17 (100)         | 0            | 16 (47.1)        | 18 (52.9)    | 0.78        |
| Current smoker                | 48 (78.7)        | 13 (21.3)    | 0.06             | 24 (45.3)    | 29 (54.7)    | 1        |
| Pack years                    |                  |              |                  |              |
| Mean±SD                       | 27.1±7.5         | 27.3±4.8     | 0.93             | 37.1±10.3    | 36.2±11.5    | 0.72     |
| Occupation                    |                  |              |                  |              |
| Heavy Work                    | 68 (82.9)        | 14 (17.1)    | ref              | 40 (47.6)    | 44 (52.4)    | ref      |
| Non-Heavy Work                | 16 (88.9)        | 2 (11.1)     | 0.73             | 7 (43.7)     | 9 (56.3)     | 0.78     |
| Education                     |                  |              |                  |              |
| Illiterate                    | 4 (80)           | 1 (20)       | ref              | 1(50)        | 1(50)        | ref      |
| Primary School                | 77 (85.6)        | 13 (14.4)    | 0.56             | 43(45.7)     | 51(54.3)     | 1        |
| High School                   | 3(60)            | 2(40)        | 1                | 2(66.7)      | 1(33.3)      | 1        |
| Degree                        | 0(0)             | 0(0)         | 1(100)           | 0(0)         | 0.31        |
| Charlson’s comorbidity score  |                  |              |                  |              |
| Mean±SD                       | 1.35±1           | 1.25±1.1     | 0.69#            | 1.5±1.1      | 1.4±1.2      | 0.74#    |
| 0–1                           | 46 (82.1)        | 10 (17.9)    | ref              | 20 (41.7)    | 28 (58.3)    | ref      |
| 2–4                           | 38 (86.4)        | 6 (13.6)     | 0.57             | 27 (51.9)    | 25 (48.1)    | 0.31     |
| Standard of living index (SLI)|                  |              |                  |              |
| Mean±SD                       | 19.2±3           | 19.1±3.1     | 0.83             | 19.5±2.5     | 19.9±2.6     | 0.45     |
| Body Mass Index (BMI)         |                  |              |                  |              |
| Mean±SD                       | 21.7±2.2         | 22.3±2.4     | 0.32             | 19.3±2.9     | 20.6±3.3     | 0.043    |
| 18.5-22.9 (normal)            | 58 (86.6)        | 9 (13.4)     | ref              | 23 (48.9)    | 24 (51.1)    | ref      |
| Variables | Non-COPD (n=100) | COPD (n=100) | P-value | Non-COPD (n=100) | COPD (n=100) | P-value |
|-----------|------------------|--------------|---------|------------------|--------------|---------|
| Anxiety or depression | No/Minimal (n=84) | Mild/Moderate (n=16) | 1 | No/Minimal (n=47) | Mild/Moderate (n=53) | 0.6 |
| <18.5 (underweight) | 7 (87.5) | 1 (12.5) | 1 | 19 (54.3) | 16 (45.7) | 0.6 |
| 23–24.9 (overweight) | 14 (70) | 6 (30) | 0.09 | 4 (36.4) | 7 (63.6) | 0.5 |
| 25–30 (pre-obese) | 5 (100) | 0 (0) | 1 (14.3) | 6 (85.7) | 0.12 |

Baseline Vitamin D levels (ng/mL)

| Mean±SD | p-value | Mean±SD | p-value |
|---------|---------|---------|---------|
| >20 | 43 (82.7) | 9 (17.3) | 0.7 | 29 (37.7) | 48 (62.3) | 0.00077 |
| ≤20 (deficiency) | 43 (82.7) | 9 (17.3) | 0.7 | 29 (37.7) | 48 (62.3) | 0.00077 |

Six minute walk test (% predicted)

| Mean±SD | p-value | Mean±SD | p-value |
|---------|---------|---------|---------|
| FVC % predicted | 90.4±6.3 | 91.1±4.8 | 0.7 | 69.2±17.8 | 56.8±15.8 | 0.0005 |
| FEV1 % predicted | 94.4±3.6 | 94.5±4.2 | 0.89 | 55.9±16.3 | 43.3±14.6 | 0.0002 |
| FEV1/FVC Ratio | 80.9±2.7 | 80.5±2.8 | 0.53 | 64.5±6.3 | 61.1±8.9 | 0.029 |

In logistic regression analyses (Table 3c and 3d) with anxiety and depression as binary outcomes, these associations remained unchanged. Vitamin D deficiency, presence of COPD, lung function variables and six-minute walk distance had independent association with the dependent variables Mild/Moderate anxiety, depression and anxiety/depression. Vitamin D deficiency had adjusted odds ratio (95%CI) of 6.84 (2.24–20.8; p<0.001), 3.66 (1.51–8.9; p=0.004) and 4.34 (1.9–9.8; p<0.001); whereas COPD had adjusted odds ratio (95%CI) of 5.2 (1.7–15.9; p=0.004), 6.2 (2.1–18.1; p<0.001) and 4.36 (1.7–11.1; p=0.002), respectively, for Mild/Moderate anxiety, depression and anxiety/depression. Subgroup analysis for COPD group showed that vitamin D deficiency, breathlessness, GOLD staging, CAT Score, SGRQ-C symptom score and presence of exacerbations had independent association with the dependent variables Mild/Moderate anxiety, depression and anxiety/depression. Vitamin D deficiency had adjusted odds ratio (95%CI) of 4.18 (1.07–16.21; p=0.039), 5.05 (1.44–17.6; p=0.012) and 5.99 (1.83–1936; p=0.003); whereas presence of exacerbation of COPD had adjusted odds ratio (95%CI) of 17.1 (4.6–62.8; p<0.001), 13.54 (3.78–48.43; p<0.001) and 29.2 (5.7–149.2; p<0.001), respectively, for Mild/Moderate anxiety, depression and anxiety/depression.

Discussion

We conducted an investigation into the severity of anxiety and depression in subjects with COPD and age-gender matched controls, evaluated the association of anxiety and depression scores with COPD, respiratory symptoms, lung functions, vitamin D levels and exacerbation of COPD. We observed that subjects with COPD had nearly twice the mean scores of anxiety and depression as compared to non-COPD subjects. Higher respiratory symptoms (mMRC, CAT), lower lung functions (FVC, FEV1), lower vitamin D levels and higher exacerbations were associated with higher anxiety and depression scores. Higher SGRQ-C Symptom scores were associated with higher anxiety and depression scores, but the SGRQ-C Impact scores did not have an association.
Figure 1. Scatterplots for HAM-A Scores with other variables. Figures (1a–1i) are with separate markings for non-COPD and COPD subjects. Figures (1j–1n) are for COPD subjects only. Non-COPD subjects are denoted by ◯ symbol (circle) and dotted trend line. COPD subjects are denoted by ∆ symbol (triangle) and solid trend line.

Our analyses show that among the subjects with COPD, 38% and 44% had mild to moderate anxiety and depression, while 8% and 9% of non-COPD subjects had mild anxiety and depression respectively. Several studies - both large and small - corroborate the above findings. In a study consisting of 242 subjects with COPD, around 50% of the subjects had symptoms of anxiety or depression and around 1/3 of the subjects had symptoms of both. A meta-analysis which included nearly 40000 subjects each in both COPD and control groups observed that the prevalence of depression was 24.6% (95% CI
Figure 2. Scatterplots for HAM-D Scores with other variables. Figures (2a–2i) are with separate markings for non-COPD and COPD subjects. Figures (2j–2n) are for COPD subjects only. Non-COPD subjects are denoted by ◯ symbol (circle) and dotted trend line. COPD subjects are denoted by ∆ symbol (triangle) and solid trend line.

20–28.6%) in COPD group, whereas the control group had the prevalence of 11.7 (95% CI 9–15.1%)\(^3\). In a systematic review of controlled studies with more than 5000 subjects each in COPD and control groups, the depression was observed in 27.1% (25.9–28.3) in COPD subjects and 10.0% (9.2–10.8) in the control group.\(^3\) These figures emerge even after recognising and accounting for the variability in prevalence of depression across the eight studies pooled and under consideration. Similarly, in a systematic review of 10 studies, the prevalence of anxiety was 13–46%.\(^3\) This review also highlighted the prevalence and lack of study of specific anxiety disorders such as social and specific phobia and panic disorder the latter two
Figure 3. Boxplots showing the levels of Anxiety (HAM-A) and Depression (HAM-D) among COPD subjects categorized based on (a) severity of airflow limitation, (b) severity of breathlessness, (c) exacerbations of COPD and (d) in Multidimensional assessment ABCD groups of COPD. HAM-A: Hamilton Anxiety rating scale; HAM-D: Hamilton Depression rating scale; GOLD: Initiative for Chronic Obstructive Lung Disease; mMRC grade: Modified Medical Research Council grade. For (d) no subjects were in C group.
Table 3. Multiple Linear regression analysis models with Hamilton rating scale for Anxiety (HAM-A) and Hamilton rating scale for Depression (HAM-D) scores as dependent variables.

**a: presence of COPD, FVC %Pred (post), FEV1 %Pred (Post), FEV1/FVC Ratio and Six Minute Walk Distance %Pred as independent variables.**

| Model | Independent Variables                  | HAM-A |        |        |        |        |        |        |        |        |        |        |        |
|-------|----------------------------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| 1     | COPD                                   | 3.5(2.4, 4.65) | 6.206 | 0.000 | 4.4(3.2000, 5.718) | 0.547 | 0.000 |
| 2     | FVC %Pred (Post)                       | -0.092 (-0.117, -0.067) | -0.507 | 0.000 | -0.106 (-0.135, -0.077) | -0.494 | 0.000 |
| 3     | FEV1 %Pred (Post)                      | -0.082 (-0.101, -0.062) | -0.604 | 0.000 | -0.099 (-0.120, -0.077) | -0.619 | 0.000 |
| 4     | FEV1/FVC Ratio (Post)                  | -0.184 (-0.229, -0.139) | -0.587 | 0.000 | -0.240 (-0.289, -0.191) | -0.648 | 0.000 |
| 5     | Six minute walk distance %Pred         | -0.088 (-0.122, -0.055) | -0.413 | 0.000 | -0.117 (-0.155, -0.079) | -0.464 | 0.000 |

**b: presence of breathlessness, mMRC breathlessness grade, Global Initiative for Obstructive Lung Diseases (GOLD) FEV1 staging, COPD Assessment Test (CAT) score, St. George Respiratory Questionnaire-COPD (SGRQ-C) scores (SGRQ-C Total, SGRQ-C Symptom, SGRQ-C Activity, SGRQ-C Impact), history of COPD exacerbations and number of exacerbations as independent variables.**

| Model | Independent Variables                  | HAM-A |        |        |        |        |        |        |        |        |        |        |        |
|-------|----------------------------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| 1     | Breathlessness                         | 3.1(1.66, 4.66) | 0.452 | 0.000 | 2.7 (0.96, 4.5) | 0.323 | 0.003 |
| 2     | mMRC Breathlessness Grade             | 1.926 (1.034, 2.818) | 0.459 | 0.000 | 2.272 (1.274, 3.270) | 0.449 | 0.000 |
| 3     | GOLD FEV1 Staging                     | 1.934 (1.089, 2.780) | 0.417 | 0.000 | 2.004 (1.028, 2.980) | 0.358 | 0.000 |
| 4     | CAT Score                              | 0.243 (0.132, 0.355) | 0.396 | 0.000 | 0.264 (0.137, 0.392) | 0.356 | 0.000 |
| 5     | SGRQ-C Total                           | 0.156 (0.023, 0.288) | 0.230 | 0.022 | 0.099 (-0.054, 0.252) | 0.121 | 0.203 |
| 6     | SGRQ-C Symptom                         | 0.091 (0.031, 0.151) | 0.294 | 0.003 | 0.090 (0.021, 0.159) | 0.242 | 0.011 |
| 7     | SGRQ-C Activity                        | 0.072 (-0.013, 0.157) | 0.177 | 0.096 | 0.102 (0.007, 0.197) | 0.209 | 0.036 |
| 8     | SGRQ-C Impact                          | 0.029 (-0.071, 0.130) | 0.059 | 0.563 | -0.050 (-0.164, 0.063) | -0.084 | 0.379 |
| 9     | Presence of COPD Exacerbations         | 3.79 (2.56, 5.02) | 0.537 | 0.000 | 4.24 (2.84, 5.63) | 0.497 | 0.000 |
| 10    | Number of Exacerbations                | 2.268 (1.839, 2.698) | 0.768 | 0.000 | 2.568 (2.083, 3.053) | 0.721 | 0.000 |

**c: presence of COPD, FVC %Pred (post), FEV1 %Pred (Post), FEV1/FVC Ratio and Six Minute Walk Distance %Pred as independent variables.**

| Model | Independent Variables                  | Mild/Moderate Anxiety |        |        |        | Mild/Moderate Depression |        |        |        | Mild/Moderate Anxiety or Depression |        |
|-------|----------------------------------------|-----------------------|-------|-------|-------|--------------------------|-------|-------|-------|-------------------------------------|-------|
|       |                                        | Adjusted Odds Ratio (95%CI) | P-Value | Adjusted Odds Ratio (95%CI) | P-Value | Adjusted Odds Ratio (95%CI) | P-Value |
| 1     | COPD                                   | 5.2(1.7-15.9) | 0.004 | 6.2(2.1-18.1) | 0.000 | 4.3(1.7-11.1) | 0.002 |
| 2     | FVC %Pred (Post)                       | 0.95(0.92-0.97) | 0.000 | 0.95(0.93-0.97) | 0.000 | 0.95(0.93-0.98) | 0.000 |
| 3     | FEV1 %Pred (Post)                      | 0.96(0.93-0.98) | 0.000 | 0.96(0.93-0.97) | 0.000 | 0.96(0.94-0.98) | 0.000 |
of which were particularly seen more in women. Another study, conducted in Nepal with 93 COPD subjects and 105 controls, observed around 2–3 times higher mean anxiety and depression scores in COPD subjects compared to controls.36

Despite the diversity in the scales chosen to measure and evaluate anxiety and depression – such as Beck Anxiety and Depression Inventory Scale, HAM-A and HAM-D – across all the above studies, the common undercurrent among them points to a striking prevalence of the disorders among subjects with COPD than without. Though the full details and association between anxiety, depression and COPD remains as yet unclear, various factors have been touted as responsible for this link.

Foremost among them is smoking.37 The effects that smoking and depression have on one-another is mirrored in nature. While on one hand smokers tend to have an increased susceptibility to developing COPD (prevalence ranges from about 15–50%), and hence depression, depressed subjects tend to have a higher inclination to smoke. A comprehensive review of about 297 articles by 39 states that depressed individuals actively seek out smoking in order to try and mitigate the increased levels of distress, cognitive impairment and low levels of environmental interaction that they tend to face. Increased levels of acetylcholine have been associated with depressive symptoms.39 Since smoking is linked to the activation of nicotinic acetylcholine receptors, depression symptoms manifest.35

### Table 1: Effect of COPD on Anxiety and Depression

| Model | Independent Variables | Mild/Moderate Anxiety | P-Value | Mild/Moderate Depression | P-Value | Mild/Moderate Anxiety or Depression | P-Value |
|-------|-----------------------|-----------------------|---------|--------------------------|---------|-----------------------------------|---------|
| 4     | FEV1/FVC Ratio (Post) | 0.91(0.86-0.96)       | 0.000   | 0.85(0.77-0.93)          | 0.000   | 0.92(0.89-0.96)                   | 0.000   |
| 5     | Six minute walk distance %Pred | 0.94(0.92-0.97) | 0.000   | 0.94(0.91-0.97)          | 0.000   | 0.94(0.91-0.97)                   | 0.000   |

### Table 2: Effect of COPD on Anxiety and Depression

| Model | Independent Variables | Mild/Moderate Anxiety | P-Value | Mild/Moderate Depression | P-Value | Mild/Moderate Anxiety or Depression | P-Value |
|-------|-----------------------|-----------------------|---------|--------------------------|---------|-----------------------------------|---------|
| 1     | Breathlessness        | 43.98(5.13-376.6)     | 0.000   | 10.67(2.8-40.1)          | 0.000   | 24.9(5.8-107.5)                   | 0.000   |
| 2     | mMRC Breathlessness Grade | 7.98(2.51-25.3) | 0.000   | 5.27(1.88-14.72)         | 0.002   | 8.7(2.6-29)                      | 0.000   |
| 3     | GOLD FEV1 Staging     | 3.69(1.56-8.71)       | 0.003   | 4.7(1.84-12)             | 0.002   | 4.02(1.6-10.2)                   | 0.004   |
| 4     | CAT Score             | 1.18(1.05-1.32)       | 0.004   | 1.13(1.02-1.24)          | 0.015   | 1.13(1.02-1.25)                  | 0.015   |
| 5     | SGRQ-C Total          | 1.1(0.99-1.22)        | 0.058   | 1.06(0.96-1.16)          | 0.26    | 1.1(0.99-1.24)                   | 0.056   |
| 6     | SGRQ-C Symptom        | 1.07(1.01-1.13)       | 0.018   | 1.08(1.02-1.14)          | 0.007   | 1.09(1.02-1.15)                  | 0.007   |
| 7     | SGRQ-C Activity       | 1.04(0.97-1.11)       | 0.23    | 1.06(0.99-1.13)          | 0.1     | 1.05(0.98-1.13)                  | 0.15    |
| 8     | SGRQ-C Impact         | 1.03(0.95-1.11)       | 0.48    | 0.97(0.89-1.04)          | 0.36    | 1.01(0.93-1.1)                   | 0.743   |
| 9     | Presence of COPD Exacerbations | 17.1(4.6-62.8) | 0.000   | 13.54(3.78-48.43)        | 0.000   | 29.2(5.7-149.2)                  | 0.000   |
| 10    | Number of Exacerbations | 10.01(3.54-28.3) | 0.000   | 6.16(2.51-15.12)         | 0.000   | 14.59(3.5-60.5)                  | 0.000   |

(All the regression models were adjusted for Age, Body Mass Index (BMI), Charlson’s Co-morbidity Index Score (CCI Score), Standard of living Index (SLI), Smoking Pack Years and vitamin D levels)
Of the subjects with COPD who do not smoke, biomass smoke exposure, which about 3 billion people are exposed to worldwide, is acknowledged as a major risk factor. The burning of biomass releases a variety of harmful pollutants such as methane and volatile organic compounds, nitrogen oxides, sulphur oxides, hydrogen chloride, poly-aromatic hydrocarbons, furans and dioxins, organic and inorganic aerosol particulates known as particulate matter. Biomass smoke exposure has been linked to both the decrease in pulmonary antimicrobial defence as well as the mediation of lung immune modulation by surface cell receptors such as PRRs and TRPs. Though the exact mechanism of the latter is well explored with respect to cigarette smoke, it is yet to be as extensively explored with respect to biomass smoke. Like cigarette smoke, biomass smoke also increases lung inflammation and leads to tissue proliferation in small airways and tissue destruction in lung parenchyma. Lung inflammation “overspill” into the circulatory system has been postulated as a possible reason for increased prevalence of depression among subjects. sTNFR-1 and TNF-α are 2 indicators that are associated with increased depression though this association is as yet inconsistent. Another as yet inconsistent factor is low arterial oxygen concentration caused by hypoxia. The most influential factor, however, is the severity of COPD symptoms themselves and the reported quality of life. A perception of dependency for basic life activities shows an association with depression. Similarly, for anxiety, a traumatic event causing a sensitization (behavioural sensitization event) – such as that caused by a COPD associated exacerbation – leads to an increased risk of developing panic disorders. Should such a disorder develop, a misinterpretation of a bodily event can lead to a panic attack. Moreover, events such as hyperventilation and dyspnoea lead to an abnormality in concentration of CO2 (pCO2). Due to this, areas containing CO2/H+-sensitive neurons such as the ventro-lateral surface of the medulla and locus coeruleus that are involved in ventilation as well as panic behaviours may get activated and trigger panic attacks.

Overall, symptoms associated with COPD, anxiety and depression serve as triggering factors for one another in a continuous vicious cycle that can escalate to even be fatal. A classic display of this triangular interplay is seen in psychoneuroimmunology with respect to COPD. Psychoneuroimmunology is the study of the relationship between the nervous system, the endocrine system and the immune system. It highlights the way in which neurotransmitters and hormones communicate with the immune system while the immune system communicates with the nervous system through cytokines. COPD associated inflammation has links to an increase in the presence of cytokines in blood plasma which in turn has been shown to induce symptoms of depression. The activation of dorsal anterior cingulate cortex – linked to anxiety - could contribute to these behavioural symptoms caused by cytokines. Interferon-alpha has been shown to affect serotonin synthesis and uptake and impact behaviour. It was found that serotonin reuptake inhibitors were effective in preventing interferon-alpha induced depression. Furthermore, a link between decreased dopamine levels, interferon-alpha induced depressive symptoms and basal ganglia was also found.

A common reason for anxiety and depression in COPD subjects causing an increased risk of mortality is non-compliance with treatment procedures prescribed by their doctors and caregivers. This non-compliance is three times more likely as compared a subject without anxiety and depression. Other contributing factors are continuation of smoking, poor nutrition and increased stress.

An extension of association between COPD and anxiety and depression highlights the interlink between respiratory symptoms and anxiety and depression. A study with 35 subjects with COPD found that the subjects with lower lung function, higher symptoms and exacerbations had higher HAM-A and HAM-D scores. The study also showed that combined respiratory and psychotic therapy greatly mitigated symptoms – both respiratory and psychological. Another study, while looking at the differences in anxiety and depression scores among male and female COPD subjects with similar CAT scores, also showed that among the total 128 COPD subjects, lower CAT scores was associated with lower anxiety and depression scores. It was also observed that the higher anxiety and severe scores were observed in subjects with higher dyspnoea grades, lower six-min walk distance, lower lung function and higher exacerbation numbers.

There are also studies that highlight the association of anxiety and depression with a particular phenotype of COPD – its exacerbations. COPD patients with depressive symptoms were 2.8 (1.1-7.3; p=0.03) times more likely to have exacerbations and suffered the first exacerbation earlier compared to patients without depressive symptoms. Another study that reported results of a three-year longitudinal follow-up of the ECLIPSE Cohort, with a participant size of 2095 showed that higher depressive symptoms were related to increased risk of exacerbations with odds ratio of 1.18 (1.07-1.3). This increased risk also leads to an increased frequency of hospitalization (adjusted IRR, 1.72; 95% CI, 1.04-2.85) and exacerbations also tend to last 1.92 (1.04-3.54) times longer for patients with probable anxiety than those with no anxiety. Similarly, in a systematic review, 20 studies had observed an association of anxiety and depression with exacerbation and hospitalization. In a study with 521 subjects, 15.6 subjects had either anxiety or depression. Anxiety and depression were strongly associated with frequent exacerbation while also highlighting other risk factors for exacerbation such as obesity, being overweight and diabetes. Studies have shown that the presence of depression and anxiety compound the already debilitating effects and costs of COPD driven exacerbations. It has been seen that these costs, usually associated with hospitalization, increase to $23,759 versus $17,765 per patient, due to the presence of these mental health disorders. Depression causes patients to be 77% more likely to have a COPD-related hospitalization, 48% more likely to have an emergency room visit, and 60% more likely to have a hospitalization/emergency room visit compared with COPD patients without comorbid depression. Similarly, anxiety has been found to increase the likelihood of exacerbations, more frequent relapses and subsequent hospitalizations. Conversely, it has been found by Howard et al that an inclusion of psychologically backed treatments to existing
treatments targeting COPD, led to substantial reductions in these hospitalisation costs\textsuperscript{33,34}. While it is not fully established in what exact way depression causes increased exacerbations, there are some plausible explanations. This could be depression leading to a lowering of immunity which can increase the ease with which COPD patients may fall prey to environmental pathogens and pollutants\textsuperscript{35}. While most people with COPD manage to adapt to the changing life circumstances, this adaptability is impaired in people with depression\textsuperscript{36}. They may also be less inclined to comply with treatment and medication schedules leading to poorer quality of care\textsuperscript{37}.

Epidemiologic studies, mechanistic studies have confirmed that Vitamin D deficiency causes depression and anxiety. Several epidemiologic studies have demonstrated that Vitamin D deficiency is associated with depression\textsuperscript{23,34}. Vitamin D deficiencies are known to increase depression by 8–14\%. Major depression is also increased, with an increase in suicides of 50\% in Vitamin D deficient subjects. In a large longitudinal study (35,000) subjects, patients with severe COPD had twice the risk of developing depression as compared to mild COPD and depression was observed in 16.2 cases per 1000 person-years in COPD subjects and 9.4 cases per 1000 person-years in non-COPD subjects\textsuperscript{38}. The prevalence of anxiety in COPD subjects may range from 13–46\%. Though many studies have confirmed association, further studies are needed to confirm causation. Meta-analysis of Vitamin D supplementation clinical trials failed to show benefit when all the studies were considered. However, several of those studies had biological flaws including using ineffective dose of Vitamin D, use of calcium instead of Vitamin D, including patients with depression without Vitamin D deficiency, that could have influenced a negative result. When only studies without biological flaws were considered, the effect size was similar to that of anti-depressants, which suggest a very potent effect of Vitamin D\textsuperscript{39}. A clinical trial of Vitamin D supplementation for 6 months observed an improvement in anxiety but not depression as compared to controls. Further larger studies are needed to confirm these findings, which have not always been consistent\textsuperscript{40}.

The hypotheses on how Vitamin D deficiency affects mood disorders such as depression and anxiety are manifold. Mechanistic studies have confirmed the presence of enzymes for hydroxylisation for the conversion of Vitamin D to its active form (1,25 dihydroxy vitamin D) in the hypothalamus, substantia nigra and cerebellum. Vitamin D prevents depletion of serotonin and dopamine in the central nervous system and modulates the hypothalamo-pituitary-adrenal axis. Vitamin D increases the serotonin levels by increasing gene expression of serotonin synthesizing enzymes tryptophan hydroxylase 1 and 2. Vitamin D influences calcium metabolism and can profoundly affect mood disorders\textsuperscript{37}. Through the Vitamin D receptors in the adrenal cortex Vitamin D acting as a coenzyme influences systemic levels of adrenalin, dopamine and noradrenaline. Smoking, systemic inflammation and hypoxia in COPD patients contribute to higher rates of depression and anxiety in COPD patients than the general population\textsuperscript{37}. Low grade systemic inflammation is observed in both patients with COPD and mood disorders such as depression and anxiety. Vitamin D levels are critical for enhancing the glutamate and glutamine metabolism in neurons and can cause neurotransmitter alterations influencing behavior disorders. Vitamin D leads to an up-regulation of transient receptor potential vanilloid calcium-selective cation channels, (TRPV5, TRPV6) in the brain. Vitamin D levels are also important for promoting antioxidant defenses in neurons and increase gene expression of neurotrophic factors that stimulate neurogenesis. Vitamin D levels thus are shown to influence brain development, neuroplasticity and neuro-immunomodulation via multiple pathways\textsuperscript{42}

Strengths and limitations
This is a well characterised community cohort with a follow-up of six months, included controls from the general population who were age and gender matched. Vitamin D levels were measured twice during the study at an interval of 6 months in two seasons to assess any differences during winter. HAM-A and HAM-D scores were assessed twice to assess stability of scores over time. The main limitation of our study was the relatively small sample size. We did not supplement Vitamin D to assess whether anxiety and depression would be improved. The sub-group analysis of different COPD severity as well as anxiety and depression had smaller number of subjects. There were no subjects in group C of COPD (multidimensional categorization ABCD). There were no subjects either in the COPD group or general population who had severe anxiety and depression and thus results are not generalizable to those patients.

Conclusion
A greater proportion of COPD subjects suffer from anxiety and depression as compared to subjects without COPD. The severity of anxiety and depression was also greater in COPD subjects. Poorer lung functions, higher respiratory symptoms such as dyspnoea and lower Vitamin D levels are associated with more severe anxiety and depression in COPD patients. There is an urgent need to recognise and treat depression and anxiety in those with COPD.

Data availability
Underlying data
Open Science Framework: Data of the project Vitamin D, Anxiety (HAM-A), Depression (HAM-D) in COPD and controls, https://doi.org/10.17605/OSF.IO/4NM7H\textsuperscript{43}.

The data is available in two file formats as follows:

- COPD HAM Vitamin D - Data for Repository.csv (CSV Format)
- COPD HAM Vitamin D - Data for Repository.xlsx (XLSX Format)
- Header and Key detail for the data file.csv (CSV Format)
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Extended data

Open Science Framework: Data of the project Vitamin D, Anxiety (HAM-A), Depression (HAM-D) in COPD and controls, https://doi.org/10.17605/OSF.IO/4NM7H*. This project contains the following extended data files:

- Supplement Table e1a: Correlation Coefficient (R) and p values for HAM-A and HAM-D with other variables, grouped as Non-COPD and COPD.
- Supplement Table e1b: Correlation Coefficient (R) and p values for HAM-A and HAM-D with other variables, among COPD Subjects.
- Supplemental Figure e1: Flow chart showing subject recruitment in this study.

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

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