

# Relationship between depression and anxiety, health status and lung function in patients with Alpha-1 Antitrypsin deficiency

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## ORIGINAL RESEARCH

### **Relationship between Depression and Anxiety, Health Status and Lung Function in Patients with Alpha-1 Antitrypsin deficiency**

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**Author contributions:** FM and AMT were instrumental in the conception and design of the study and FM, AMT, RE, AP and RAS contributed towards data acquisition, analysis and interpretation. All authors contributed to drafting and critically revising the paper and approved the final submitted version.

## **Abstract**

Alpha-1 Antitrypsin deficiency (AATD) is a genetic condition that can lead to Chronic Obstructive Pulmonary Disease. The burden of psychological disease, its impact and contributing factors in patients with AATD are largely unknown. This study determined the prevalence of depression and anxiety in AATD and its clinical impact. All subjects with PiZZ/PiZnull (n = 635) and PiSZ (n = 111) genotypes within the AATD registry who had sufficient data to calculate pulmonary physiological and health status (HS) decline were grouped as those with or without a diagnosis of depression and/or anxiety. Univariate and multivariate analyses were performed on physiological, demographic and HS parameters. Depression and/or anxiety was present in 16.4% overall in both PiSZ and PiZZ/PiZnull cohorts and was associated with lower baseline pulmonary function and worse HS. In the multivariable analysis of the PiZZ/PiZnull cohort, a greater average decline in FEV<sub>1</sub>% predicted was observed in those with depression and/or anxiety than those without ( $-1.53 \text{ SD} \pm 2.26$  per year,  $-0.99 \pm 1.79$ , respectively;  $p = 0.03$ ) but there was no difference in HS decline ( $p = 0.33$ ). No differences were seen in the PiSZ cohort. Dyspnea (mMRC score) was generally worse in those with depression and/or anxiety than those without. Comorbidity burden did not differ between those with or without depression and/or anxiety. Disease severity and progression may be contributing to the prevalence of psychological factors in PiZZ/PiZnull patients. Patients who are declining rapidly should be actively monitored for psychological co-morbidity and treated by cognitive or pharmacological means.

**Keywords:** Alpha-1 Antitrypsin Deficiency, Depression, Anxiety, Lung Function, Health Status, Comorbidities, Antidepressants

## **Introduction**

Alpha-1 Antitrypsin deficiency (AATD) is a genetic condition that increases susceptibility to Chronic Obstructive Pulmonary Disease (COPD), and also Liver disease [1], Bronchiectasis [2], Vasculitis [3], Panniculitis [4] and Inflammatory Bowel Disease [5]. It is clinically characterised by symptoms of chest tightness, wheezing, increased cough, sputum production and shortness of breath [6]. Whilst pulmonary emphysema is the most common manifestation in AATD, there are differences in the development of emphysema from individuals with usual non-deficient COPD. This difference reflects the distribution and the enhanced susceptibility to damage which presents at a younger age in AATD patients [7]. Early onset of pulmonary disease at a younger age and more generally active stage of life could therefore be associated with worse psychological as well as clinical outcomes [8].

Psychological problems have been recognised and widely studied in patients with COPD, with a systematic review showing a general prevalence of 27% for depression and a relationship between depression or anxiety and poor health status [9]. However the psychological impact and contributing factors in patients with AATD, many of whom have COPD at younger age than non-deficient patients, are largely unknown. In non-deficient COPD depression and anxiety are associated with an impact on everyday activities, more severe symptoms (e.g. shortness of breath and fatigue) [10], increased hospitalisation, mortality and morbidity rates, as well as non-compliance with treatment [11]. Furthermore, undiagnosed depression and anxiety in COPD patients may also impair social interactions, physical functioning and lead to a downward psychological spiral and increased use of healthcare systems [10,12].

Increased feelings of panic, fear and hopelessness in addition to dyspnoea and fatigue, may amplify a cycle that modulates anxiety and depression [13]. The overlap of COPD and depression and anxiety symptoms highlights the challenges for diagnosing and treating coexistent psychological disorders [14].

In COPD, reduced lung function (specifically FEV<sub>1</sub> – forced expiratory volume in 1 second) is related to health status and mortality rates [15-17] therefore slowing physiological progression is a key objective of current and future therapies [18]. COPD patients have more rapid decline of lung function beyond normal ageing [18,19] especially in AATD [20].

We hypothesised that anxiety and depression would be at least as common in AATD, as in non-deficient COPD, and relate to severity and decline in lung function and health status, as well as overall co-morbidity burden. The current paper explores these possibilities in a highly characterised patient population followed prospectively in a single centre.

## **Methods**

### *Patient Characteristics*

All AATD subjects with the PiZZ, PiZnull and PiSZ genotype enrolled into the UK ADAPT AATD registry from 1996 to 2016 were included in the study. The study was approved by South Birmingham Research and Ethics Committee (LREC number: 3359) and written informed consent was obtained from all subjects. Once identified from the database, subjects were grouped into those with or without a clinical diagnosis of depression or anxiety, as documented in the medical records. Depression and/or anxiety was previously diagnosed by a Clinician or the patient's GP either by diagnostic interviews or by using psychological assessment tools.

Data collected at baseline and follow up visits has been described previously [20,21]. In brief this included medical and family history, COPD related symptoms including cough, sputum volume and colour, mMRC score (modified Medical Research Council), exacerbation history, smoking history and current status, concomitant medication and occupational status. Subjects completed COPD Assessment Test (CAT), EQ5D and SGRQ (St George's Respiratory Questionnaire) to assess annual health status.

For the current study lung function (FEV<sub>1</sub>, FVC – forced vital capacity, TLCO - transfer factor of the lungs for carbon monoxide, KCO- transfer coefficient for carbon monoxide) and HS (SGRQ) data collected at baseline and annual assessments were collated. Decline in lung function was expressed as the change of the % predicted for age, sex, height and ethnicity per year, using linear regression established for all annual data points ( $\geq$  four data points over  $\geq$  3

years) for each patient as reported previously [18]. Rapid decline in lung function (FEV<sub>1</sub> and Kco change) was expressed as the change of 1.0% predicted per year (loss of FEV<sub>1</sub> or Kco greater than >1.0% predicted per year) [22]. Abnormal lung function is expressed as predicted values <80% (FEV<sub>1</sub> and Kco).

The present study assessed data from 840 (PiZZ/PiZnull) and 111 (PiSZ) eligible subjects from an existing database as part of the ADAPT AATD registry. In the PiZZ/PiZnull cohort, a total of 205 subjects were excluded including subjects lost to follow up (n = 73) with insufficient data (<3 years) to determine decline of lung function and health status. There were no subjects excluded from the PiSZ cohort. Augmentation is not routinely available in the UK, outside of a clinical trial. None of the patients included in this cohort had received augmentation therapy as treatment or part of a clinical trial.

Charlson Comorbidity Index (CCI) was used to assess the burden of comorbidities and predict 10 year survival [23]. A higher total CCI score reflects greater disease burden and higher risk of death [24]. The mMRC dyspnea scale was used to assess restricted baseline activity due to breathlessness (dyspnea) [25].

### ***Statistical analysis***

All statistical analyses were carried out in IBM SPSS Statistics for Windows, version 24.0, Armonk, NY: IBM Corp. Univariate analyses were performed on a range of physiological, demographic and HS parameters, including (but not limited to) age, FEV<sub>1</sub>% predicted, SGRQ, as well as lung function and HS decline, to determine associations with psychological co-



morbidity. Normality was assessed by visual inspection of Q-Q plots, and normal data is reported as mean (+/- standard deviation) and nonparametric data as median and interquartile range (IQR). Comparisons of categorical groups were assessed with Fisher's exact test and Kendall's tau b test and continuous variables were assessed using Mann Whitney U tests and t-tests, respectively for PiZZ/PiZnull and PiSZ cohorts. All candidate variables were then included in a multivariable multiple regression to assess independent associations with depression and/or anxiety, with FEV<sub>1</sub>% predicted decline and SGRQ decline as the dependant variables. Variables including sex, smoking status (ever smoked/never smoked), baseline lung function such as FEV<sub>1</sub>% predicted and KCO% predicted (multicollinearity was assessed), baseline total SGRQ scores and baseline mMRC scores were adjusted to account for factors that relate to decline. A statistical significance value of  $p < 0.05$  was used for all analyses.

## Results

### *Subject characteristics*

Subjects with PiZZ/PiZnull (n = 635) and PiSZ (n = 111) AATD deficiency were included in the final analysis. A clinical diagnosis of depression and/or anxiety was present in 16.4% overall (PiZZ/PiZnull and PiSZ and cohorts combined), with 16.4% in the PiZZ/PiZnull subjects and 16.2% in the PiSZ subjects. In the PiZZ/PiZnull cohort, depression and/or anxiety was associated with lower baseline FEV<sub>1</sub> (43% predicted (34-74) v 56 (40-84); p = 0.01, respectively) and worse baseline SGRQ total (57 (34-70) v 43 (28-58); p < 0.001). In the PiSZ cohort, baseline lung function (FEV<sub>1</sub>) was also lower in those with depression and/or anxiety compared to those without (73 (48-102) v 101 (74-116); p = 0.04) as well as worse SGRQ total (54 (23-67) v 21 (8-53); p = 0.01). Baseline subject demographics, and decline in lung function and HS for both PiZZ/PiZnull and PiSZ cohorts are shown in Tables 1 and 2 respectively.

### *Smoking status in PiZZ/PiZnull and PiSZ cohorts*

In the PiZZ/PiZnull cohort, there was a higher proportion of ex-smokers amongst those with depression and/or anxiety compared to those without (83% v 70%; p < 0.01). This association was reversed in the PiSZ cohort where there were more ex-smokers in those without depression and/or anxiety (82% v 55%; p = 0.03). There were no current smokers in either the PiZZ/PiZnull or PiSZ cohort.

### ***Antidepressant use in PiZZ/PiZnull and PiSZ cohorts***

In the PiZZ/PiZnull cohort, 61% of subjects with anxiety or depression (n= 63) were on active pharmacological management for their symptoms (see supplementary data table S1). In the PiSZ cohort 72% (n = 13) were on active treatment. The most common antidepressants/anxiolytics used in both cohorts were Citalopram, Fluoxetine, Paroxetine, Sertraline and Diazepam.

### ***Breathlessness (modified MRC score) in the PiZZ/PiZnull and PiSZ cohort***

In the PiZZ/PiZnull cohort, there was a statistically significant difference in the distribution of mMRC scores ( $\tau_b = 0.140$ ,  $p < 0.001$ ) between subjects with and without depression and/or anxiety. Subjects with depression and/or anxiety tended to have higher scores, most frequently being 3 in those with psychological co-morbidity, but 1 in those without (see supplementary data table S2). In the PiSZ cohort, although there was numerically a larger proportion of patients with an mMRC score of 0 with no depression and/or anxiety (and more with depression and/or anxiety in mMRC score of 1), this was not statistically significant ( $\tau_b = -0.176$ ,  $p = 0.07$ ). Figures 1 and 2 display the distribution of mMRC scores in both PiZZ/PiZnull and PiSZ cohorts.

### ***Impact of comorbidities***

The most common co-morbidities present in subjects in both cohorts (see supplementary data table S3) were confirmed liver disease (n = 37, 9%), chronic kidney disease (n = 7, 3.6%), malignancy (n = 39, 13%) and diabetes (n = 30, 8%). The frequency distribution of CCI scores (tables 1 and 2) indicated that there were no differences in comorbidity burden between those with or without depression and/or anxiety (see supplementary data table S4) in either the PiZZ/PiZnull ( $\tau_b = -0.029$ ,  $p = 0.49$ ) or the PiSZ cohorts ( $\tau_b = -0.086$ ,  $p = 0.27$ ).

### ***Lung function and Health Status decline in PiZZ/PiZnull and PiSZ cohorts***

#### ***Univariate analyses***

The decline in FEV<sub>1</sub>% predicted per year was greater in those with established depression and/or anxiety ( $-1.53 \pm 2.26$  v  $-0.99 \pm 1.79$ ;  $p = 0.03$ ) but there were no differences in annual increase in SGRQ total score ( $0.14 \pm 3.69$  and  $0.46 \pm 2.85$ ;  $p = 0.33$ ) in the PiZZ/PiZnull cohort. There was no difference in the annual decline of FEV<sub>1</sub> % predicted for PiSZ subjects in those with or without depression and/or anxiety ( $-1.49 \pm 2.13$  v  $-0.65 \pm 2.19$ , respectively;  $p = 0.32$ ), nor worsening in total SGRQ score ( $-0.20 \pm 2.33$  v  $0.43 \pm 1.80$ ;  $p = 0.54$ ). Figures 3 and 4 display FEV<sub>1</sub> and Kco data (expressed as % predicted and the rate of decline) in patients with and without depression and/or anxiety for both the PiZZ/PiZnull and PiSZ cohorts. In every comparison, there were fewer patients with depression and/or anxiety than without. However, the proportion of patients with depression and/or anxiety compared to those without was only significantly different for Kco % predicted, where there was less depression and/or anxiety in patients with a normal Kco (12.2%) compared to those with an abnormal Kco (22.3%) ( $p = 0.02$ ).

Similar data for patients with and without spirometric COPD (as defined by GOLD [21,26]) is displayed in Figures 5 and 6, where patients have been further classified by GOLD severity.

Analysis of depression and anxiety separately in PiZZ/PiZnull cohort indicated that subjects with depression alone also had a more rapid decline in median FEV<sub>1</sub>% predicted than those without (-1.32, IQR -2.78 to -0.45 v - 0.89 IQR -1.95 to 0.02, p<0.01), but not HS decline. For subjects with or without anxiety alone, there were no differences in FEV<sub>1</sub>% or SGRQ decline.

### ***Multivariable analyses***

In the PiZZ/PiZnull cohort, after adjusting for smoking status, baseline lung function and baseline mMRC scores, multivariate analyses demonstrated that those with depression and/or anxiety still had greater decline rates (FEV<sub>1</sub>% predicted coef -0.499; 95% CI -0.895 to -0.104, R<sup>2</sup> = .057; p = 0.01) although the proportion attributable to psychological comorbidity was low (5.7%). The rate of HS decline was not independently significant following adjustment (coef -0.240; 95% CI -0.880 to 0.399; R<sup>2</sup> = .027 p = 0.46).

In the PiSZ cohort, there were no differences in FEV<sub>1</sub> or HS decline related to the presence of psychological comorbidity alone (FEV<sub>1</sub>; coef -0.053; 95% CI -1.94 to 1.84; p = 0.96, SGRQ; coef 0.499; 95% CI -1.83 to 2.83; p = 0.66). Multivariable models are described more fully in supplementary data tables S5-S8.

## Discussion

The present study of AATD subjects is consistent with observations in non-deficient COPD that those with depression and/or anxiety exhibit a higher symptom burden and are likely to have more severe disease. However, uniquely the longitudinal data indicated this was also independently associated with the subsequent rate of deterioration of lung function (decline of FEV<sub>1</sub>) in the PiZZ/PiZnull cohort. This association suggests that the perception of past (or future likelihood) has an impact irrespective of baseline disease severity, and is reflected by their depression and/or anxiety.

Greater decline in FEV<sub>1</sub>% predicted was a feature of the PiZZ/PiZnull with depression and/or anxiety even after adjustment for baseline severity and other co-variates. Given that we have shown decline tends to be linear and stable over time in individuals with AATD[17] this might indicate declining lung function contributes to development of psychological impact, particularly depression. In those with moderate AAT deficiency (PiSZ) no such relationship was seen; which may reflect lower decline rates or reduced power due to the smaller cohort size.

In the general population, studies assessing lung function and depression have proposed that it relates to reduced lung function and associated dyspnea and social isolation [27]. Whilst differences in disease severity and subsequent decline between PiZZ/PiZnull and PiSZ AATD patients are well recognised [18,28] the relationship between decline and psychological disorders is novel and likely reflects recognition that the baseline state reflects previous perceived or documented progression that persists prospectively.

Our results also indicate the psychological impact of comorbidity in AATD which has not been reported in detail previously. In a systematic review of prevalence of depression in non-deficient COPD, 27% of patients and 10% of control patients [9] had evidence of a psychological impact of comorbidity which is less in our AATD subjects (16% for depression and/or anxiety) albeit higher than in health. The reasons for this are unclear, but younger age, fewer comorbidities and potentially less social consequences of illness (e.g. isolation) may influence this outcome. Nevertheless, clinicians caring for AATD patients should be aware of the early presence of depression and anxiety which can have impact on poor quality of life, abandonment of treatment and poor compliance. A diagnosis and treatment of psychological disorders may also help to reduce hospitalisations, exacerbation rates, mortality and morbidity and improve quality of life as seen in studies of non-deficient COPD [10-12]. However further work is required to evaluate the above outcomes, as well as non-adherence to specific treatment, in AATD patients with depression and/or anxiety.

In both cohorts, impaired HS was worse in those with depression and/or anxiety at baseline although no relationship to subsequent decline was observed. Whilst studies have reported relationships between symptoms of depression and anxiety and HS [29,30], meta-analysis in non-deficient COPD indicated that other factors such as dyspnea and exercise tolerance are the important determinants of HS [31]. Consequently our adjustment for disease severity (which is strongly linked to symptomology) likely accounts for the lack of relationship with HS decline, suggesting it is more dependent on respiratory symptoms than psychological factors. This would be understandable given that the HS score used is specific to respiratory disease. In non-deficient COPD patients it has been suggested that the impact of COPD is

likely to depend on non-respiratory factors such as patient's social circumstances, expectations to coping skills and psychological wellbeing in addition to the clinical burden [32]. In our study, generic HS data, such as that derived from EQ5D, is limited as this data was added to our protocol at a later point in time, and the data that EQ5D provides is not very granular relative to other generic HS questionnaires, such as SF36 [33]. Further studies of the impact of psychological morbidity on HS in AATD may clarify this by using detailed generic questionnaires rather than disease specific ones [34].

Previous smoking was more common in those with depression and/or anxiety in the PiZZ/PiZnull cohort. Research has indicated that depression and smoking may exhibit a bidirectional association in which patients with depression are at an increased risk of smoking [35] and then find smoking cessation more challenging [35,36]. However, the interaction between psychological disorders and COPD is unlikely to be related to confounding factors such as nicotine dependence and cigarette smoking alone [37]. Furthermore, in our cohort many subjects were never smokers and almost all smokers had ceased, irrespective of presence of psychological comorbidity and no relationship was found between smoking burden and psychological morbidity.

The major strength of the current study is the number of subjects and longitudinal data available for analysis. However, it has several potential limitations. In particular the number of subjects in the PiSZ cohort was relatively small, especially in those with depression and/or anxiety group limiting comparisons between both groups. Thus the findings should be reviewed and validated in a larger cohort as available in international registries. In addition, there may be an acquisition bias as subjects may be less likely to come for repeated follow-up



either if they remain subsequently well or their psychological status is markedly impaired. Either could affect the relationship to subsequent decline in lung function and HS, as greater than four data points over 3 or more years are necessary to determine decline. It is also possible that beyond these initial 4 data points, subjects who had no depression or anxiety at baseline may have subsequently developed such changes but not been identified. It is suggested that relevant questions related to psychological health should become a part of routine care in follow up.

Also the effects of depression and anxiety were studied in subjects categorised into two categorical groups (with or without) a diagnosis which would not reflect the severity of illness (mild, moderate or severe). The use of additional psychological assessment tools such as Hospital Anxiety and Depression Scale [38], Hamilton Rating Scale [39] and Geriatric Mental Health Scale [40], may help to establish the true impact of depression and anxiety in AATD patients. In view of the prevalence of these psychological issues in AATD this is important for future studies as it is recognised that psychological issues in COPD patients may remain undiagnosed and untreated [41] leading to a manageable impact on the disease [13]. This is likely in AATD subjects, albeit partly managed in 67% were at least on appropriate therapy. Effective treatment options for psychological morbidity in COPD include Cognitive Behavioural Therapy (as the most beneficial), pulmonary rehabilitation and education, relaxation therapy including breathing exercises and mindfulness [42]. A combination of antidepressants with such therapies would be a holistic intervention which is likely to be beneficial in the management of relevant patients with AATD.

## **Conclusion**

These data suggest that disease severity and progression, as measured by the annual decline of FEV<sub>1</sub>% predicted, may be contributing to the prevalence of psychological disorders in PiZZ/PiZnull patients. This implies that patients who are declining rapidly should be actively monitored for psychological co-morbidity and treated by relevant cognitive or pharmacological means.

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## **Disclosure of interest**

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## **Data availability**

Data from this study will not be publicly available due to the terms of the patient consent to participation.

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**Table 1:** Data is shown for the PiZZ/PiZnull AATD cohort at baseline and subsequent annual decline in spirometry and HS for those with and without a clinical diagnosis of depression and anxiety

Patient characteristics	Depression/Anxiety	No Depression/Anxiety	<i>p</i>
	N= 104	N = 531	
Sex			
Male	53 (14%)	315 (86%)	
Female	51 (19%)	216 (81%)	0.13
Smoking status			
Ever smoked	86 (83%)	373 (70%)	<0.01
Never smoked	18 (17%)	158 (30%)	
Age	51 (42-58)	51 (44-59)	0.24
FEV1% predicted	43 (34-74)	56 (40-84)	0.01
TLCO% predicted	63 (47-74)	69 (53-85)	<0.01
KCO% predicted	61 (50-76)	66 (53-82)	0.02
SGRQ Total score	57 (34-70)	43 (28-58)	<0.001
CCI total score	2.00 (1.00-3.75)	2.00 (1.00-3.00)	0.49
Modified MRC score	2.00 (1.00-3.00)	2.00 (1.00-3.00)	<0.001
Change in FEV1% predicted	-1.53 (2.26 )	-.99 (1.79)	0.03
Change in total SGRQ	0.14 (3.69)	0.46 (2.85)	0.33

**Notes:** The table shows data as n (%), median (IQR) or mean (standard deviation).

**Abbreviations:** FEV<sub>1</sub>, Forced Expiratory Volume in 1 Second; TLCO, Transfer Factor of the Lungs for carbon monoxide; KCO, Transfer Coefficient for carbon monoxide; SGRQ, St George's Respiratory Questionnaire; IQR, Interquartile ranges; CCI, Charlson Comorbidity Index; MRC, Medical Research Council.

**Table 2:** Data is shown for the PiSZ AATD cohort at baseline and subsequent annual decline in spirometry and HS for those with and without a clinical diagnosis of depression and anxiety

Patient characteristics	Depression/Anxiety	No Depression/Anxiety	<i>p</i>
	N= 18	N = 93	
Sex			
Male	10 (20%)	40 (80%)	0.44
Female	8 (13%)	53 (87%)	
Smoking status			
Ever Smoked	10 (55%)	76 (82%)	0.03
Never smoked	8 (44%)	17 (18%)	
Age	65 (51-72)	62 (50-72)	0.98
FEV1% predicted	73 (48-102)	101 (74-116)	0.04
TLCO% predicted	77 (56-97)	89 (72-104)	0.18
KCO% predicted	86 (62-99)	91 (76-101)	0.16
SGRQ Total score	54 (23-67)	21 (8-53)	0.01
CCI total score	2.50 (1.00-3.25)	2.00 (.00-3.00)	0.30
Modified MRC score	1.00 (1.00-3.00)	1.00 (.00-2.75)	0.10
Change in FEV1% predicted	-1.49 (2.13)	-0.65 (2.19)	0.32
Change in total SGRQ	-0.20 (2.33)	0.43 (1.80)	0.54

**Notes:** The table shows data as n (%), median (IQR) and mean (standard deviation).

**Abbreviations:** FEV<sub>1</sub>, Forced Expiratory Volume in 1 Second; TLCO, Transfer Factor of the Lungs for carbon monoxide; KCO, Transfer Coefficient for carbon monoxide; SGRQ, St George's Respiratory Questionnaire; IQR, Interquartile ranges; CCI, Charlson Comorbidity Index; MRC, Medical Research Council.

## Figure legends

**Figure 1:** The distribution of mMRC scores in the PiZZ/PiZnull cohort in those with and without depression and/or anxiety

**Notes:** The bar chart demonstrates the proportion of mMRC scores in both groups with a higher percentage of mMRC score of 1 in those with no depression or anxiety and a higher percentage of mMRC score of 3 in those with depression and/or anxiety

**Abbreviations:** mMRC score, modified Medical Research Council score

**Figure 2:** The distribution of mMRC scores in the PiSZ cohort in those with and without depression and/or anxiety

**Notes:** The bar chart shows the proportion of mMRC scores in both groups with a higher percentage of mMRC score of 0 in those with no depression or anxiety and a higher percentage of mMRC score of 1 in those with depression and/or anxiety

**Abbreviations:** mMRC score, modified Medical Research Council score

**Figure 3:** Lung function and rate of decline in AATD subjects (PiZZ/PiZnull cohort) in those with or without depression and/or anxiety

**Notes:** Figure 3A demonstrates the number of subjects (in those with or without depression and/or anxiety) displaying normal or abnormal FEV<sub>1</sub>. Figure 3B demonstrates the number of subjects (in those with or without depression and/or anxiety) displaying rapid or non-rapid decline in FEV<sub>1</sub>. Figure 3C demonstrates the number of subjects (in those with or without depression and/or anxiety) displaying normal or abnormal Kco. Figure 3D demonstrates the number of subjects (in those with or without depression/anxiety) displaying rapid or non-rapid decline in Kco.

**Abbreviations:** FEV<sub>1</sub>, Forced Expiratory Volume in 1 Second; Kco, Transfer Coefficient for carbon monoxide; PRED, Predicted.

**Figure 4:** Lung function and rate of decline in AATD subjects (PiSZ cohort) in those with or without depression and/or anxiety

**Notes:** Figure 4A demonstrates the number of subjects (in those with or without depression and/or anxiety) displaying normal or abnormal FEV<sub>1</sub>. Figure 4B demonstrates the number of subjects (in those with or without depression and/or anxiety) displaying rapid or non-rapid decline in FEV<sub>1</sub>. Figure 4C demonstrates the number of subjects (in those with or without depression and/or anxiety) displaying normal or abnormal Kco. Figure 4D demonstrates the number of subjects (in those with or without depression and/or anxiety) displaying rapid or non-rapid decline in Kco.

**Abbreviations:** FEV<sub>1</sub>, Forced Expiratory Volume in 1 Second; Kco, Transfer Coefficient for carbon monoxide; PRED, Predicted.

**Figure 5:** Different severity stages of COPD and no COPD in those with or without depression and/or anxiety PiZZ/PiZnull cohort

**Notes:** The bar chart demonstrates the number of those with or without COPD and those with different severity stages of COPD as defined by GOLD in those with or without depression and/or anxiety.

**Abbreviations:** COPD, Chronic Obstructive Pulmonary Disease; GOLD, Global initiative for Chronic Obstructive Lung Disease

**Figure 6:** Different severity stages of COPD in those with or without depression and/or anxiety PiZZ/PiZnull cohort

**Notes:** The bar chart demonstrates the number of those with or without COPD and those with different severity stages of COPD as defined by GOLD in those with or without depression and/or anxiety.

**Abbreviations:** COPD, Chronic Obstructive Pulmonary Disease; GOLD, Global initiative for Chronic Obstructive Lung Disease