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Abstract

Background: Both of asthma and COPD affect psychological state due to their impact on general activities of patients and their ability to cause anxiety and depression. The Hospital Anxiety and Depression Scale, HADS, was designed to provide a simple and reliable tool for use in medical practice. Aim: This study aimed to evaluate the prevalence of anxiety and depression disorders in asthma and COPD patients in different Saudi Arabia localities and their relationship to pulmonary function. Patients and methods: This study included 420 subjects from three different places in KSA (Jeddah, Riyadh and AL Khobar) and were divided into three groups. Group I asthmatic patients included (150) patients, group II COPD patients included (150) patients and control group contain (120) healthy subjects. All patients were instructed to answer the questionnaire of HADS. Results: There is increased prevalence of anxiety and depression in both asthma (28%, 20%) and COPD (22%, 14%) patients in comparison to control group (16%, 4%) respectively. Anxiety was more common in females than males in asthmatics with highly significant statistical differences ($p = 0.002$) while depression was common in males than females with highly significant statistical differences ($p = 0.001$). In COPD group, anxiety and depression were more prevalent in males with highly significant statistical differences for anxiety between males and females ($p = 0.004$) and non-significant differences for depression. In (COPD) group, it was found that anxiety and depression have strong negative correlation with pulmonary function and strong positive correlation with the age, smoking index, number of exacerbations per year and duration of disease while in asthma and control groups the correlations were weak. Geographically, Anxiety and depression were more in AL-Khobar and Jeddah than Riyadh in asthmatic patients ($P = 0.01, .04$) while no significant difference in geographical distribution in COPD and control. Conclusions: Asthma and COPD patients are prone to anxiety and depression more than normal populations, this lead to poor outcomes of both diseases.

Keywords	Asthma; COPD; anxiety;depression;HADS;Saudi Arabia
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Cover letter

Title: Prevalence of anxiety and depression in patients with airway obstruction using Hospital Anxiety and Depression Scale (HADS) in different localities of Saudi Arabia

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Prevalence of anxiety and depression in patients with airway obstruction using Hospital Anxiety and Depression Scale (HADS) in different localities of Saudi Arabia

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Short title: Anxiety, depression in asthma and COPD

Summary at a Glance: This study included 420 subjects divided into three groups: Group I asthmatic (150) patients, group II COPD patients (150) and control group contain (120) healthy subjects. All patients and healthy subjects were instructed to answer the questionnaire of HADS. Anxiety and depression scales were calculated with prevalence of each. Anxiety and depression were more common in people with asthma and COPD.

Abstract:

Background: Both of asthma and COPD affect psychological state due to their impact on general activities of patients and their ability to cause anxiety and depression. The Hospital Anxiety and Depression Scale, HADS, was designed to provide a simple and reliable tool for use in medical practice. **Aim:** This study aimed to evaluate the prevalence of anxiety and depression disorders in asthma and COPD patients in different Saudi Arabia localities and their relationship to pulmonary function. **Patients and methods:** This study included 420 subjects from three different places in KSA (Jeddah, Riyadh and AL Khobar) and were divided into three groups. Group I asthmatic patients included (150) patients, group II COPD patients included (150) patients and control group contain (120) healthy subjects. All patients were instructed to answer the questionnaire of HADS.

Results: There is increased prevalence of anxiety and depression in both asthma (28%, 20%) and COPD (22%, 14%) patients in comparison to control group (16%, 4%) respectively. Anxiety was more common in females than males in asthmatics with highly significant statistical differences ($p = 0.002$) while depression was common in males than females with highly significant statistical differences ($p = 0.001$). In COPD group, anxiety and depression were more prevalent in males with highly significant statistical differences for anxiety between males and females ($p = 0.004$) and non-significant differences for depression. In (COPD) group, it was found that anxiety and depression have strong negative correlation with pulmonary function and strong positive correlation with the age, smoking index, number of exacerbations per year and duration of disease while in asthma and control groups the correlations were weak. Geographically, Anxiety and depression were more in AL-Khobar and Jeddah than Riyadh in asthmatic patients ($P=0.01, .04$) while no significant difference in geographical distribution in COPD and control.

Conclusions: Asthma and COPD patients are prone to anxiety and depression more than normal populations, this lead to poor outcomes of both diseases.

Keywords: Asthma, COPD, anxiety, depression, HADS

Background:

Patients with asthma and chronic obstructive pulmonary disease represent the majority of patients attending pulmonary outpatient clinics and also attending frequently the primary care clinics. Asthma is an inflammatory disorder of the airways that many inflammatory cells and multiple mediators that result in characteristic pathophysiological changes take apart. Asthma is characterized by persistent airway inflammation with episodic symptoms [1]. Chronic Obstructive Pulmonary Disease (COPD) is a common preventable and treatable disease. It is characterized by progressive persistent airflow limitation [2]. A concurrent psychiatric disorder including anxiety and depression may complicate the quality of life of a chronically airway obstructed patients. This may bring the patient into a vicious circle of affecting each other's [3]. On the other hand, studies show that psychiatric wellness can improve lung function response and pulmonary health [4,5]. Studies had shown that patients with asthma have double risk of developing depressive symptoms as compared with those who do not have asthma [6]. There is a controversy between asthma severity and presence of anxiety and depression despite their association [7]. Anxiety and depression are also well-recognized major comorbidities in Chronic Obstructive Pulmonary Disease [8]. It is well known that, psychiatric conditions are not regularly diagnosed in respiratory patients and are not well treated [5,9]. The awareness of the presence and severity of psychiatric disorders in patients with chronic respiratory conditions encourages patients to take the necessary measures for treatment. Psychiatric problems negatively influence disease severity and quality of life of the patients.

The Hospital Anxiety and Depression Scale, or HADS, was designed to provide a simple and reliable tool for use in medical practice.]. It was evaluated by local psychiatric group and was validated to be applied for pulmonary outpatient attendances. It is valid to be used in a hospital setting as well as in community settings and in primary care medical practice [10]

Aim of the study:

This study aimed to evaluate the prevalence of anxiety and depression disorders in asthma and COPD patients in three different Saudi Arabia localities and their correlation to pulmonary function test. Also, it aimed to give more awareness about these disorders as regards symptoms and appropriate management.

Patients and methods:

Patients: this study included four hundred twenty (420) subjects divided into three groups. Group I controlled asthmatic patients (150) patients, group II stable COPD (150) patients and control group (120) healthy subjects. They were equally distributed between three localities (Riyadh, Jeddah, ALKhobar). The inclusion criteria included, stable asthma patients, stable COPD patients older than 18 years old and patient signing a written consent for the study. Exclusion criteria included other chronic diseases, any previously diagnosed psychiatric problems, disturbed conscious level and refusal to sign the consent. Study was approved from local ethics committee.

Methods: (300) patients were recruited from pulmonary outpatient clinic from three different places in KSA (Jeddah, Riyadh and AL Khobar) during the period between October 2015 and October 2016. One hundred twenty (120) volunteer subjects were included in this study as a control group. Fifty asthmatic patients, fifty COPD patient s and forty healthy control subjects were investigated in each locality. Informed written

consent was obtained from each subject after explaining the purpose of the study to him/her.

All the three groups underwent full history taking including history of smoking (current, ex, and non-smoking), history of chest symptoms (cough, expectoration, wheezes and dyspnea), and number of exacerbation in the last year and history of any other co morbidities. Also, thorough clinical examination, general and local respiratory system examination was done. The average number of exacerbation per year and duration of illness was calculated in the previous 5 years and average was taken.

Physiological assessment was also done using spirometry. Flow/volume loop was performed to all cases. The test was done before and 20 min. after 2 puffs of Salbutamol (200 µg) via a metered dose inhaler. All data were expressed in percent of predicted value (FEV1%, FVC%, FEV1/FVC %).

Diagnosis of asthma was made according to GINA 2015:

Clinical criteria:

Symptoms of Wheeze, shortness of breath, chest tightness and cough which are variable over time and variable in intensity, worse at night or in the early morning, Often triggered by exercise, laughter, allergens, cold air. Symptoms are worsened with viral infections

Spirometric criteria:

Positive bronchodilator (BD) reversibility test

At least once during diagnostic process when FEV1 is low, reduced FEV1/FVC, increase in FEV1 of >12% and >200 mL from baseline, 10–15 minutes after 200–400 mcg salbutamol. [11],

controlled asthma was defined as the need for rescue medications twice or less a week (short-acting b2-agonists), no limitation of daily activity, no nocturnal symptoms, twice or less a week, daytime symptoms, and forced expiratory volume in the first second (FEV1)% greater than 80% predicted. There were no exacerbations (needing hospital admission or ER visit).

On the other hand, diagnosis of COPD was relayed on GOLD criteria for COPD diagnosis

Clinical criteria;

In patients above 40 years:

Symptoms of persistent progressive dyspnea worse on exercise

Chronic cough usually productive but may be non- productive

History of risk factors mostly tobacco smoking

Spirometric criteria

Non reversible airflow limitation with post-bronchodilator FEV1/FVC <70% after 200-400 mcg salbutamol [12]

Patients were stable not in exacerbation or need for hospital admission or ER visit.

Hospital Anxiety and Depression Scale (HADS): All patients had completed the questionnaire of German version of the hospital anxiety and depression scale [13,14]. It measures anxiety and depression in outpatient settings. It contains 14 statements describing symptoms of anxiety and depression, seven statements for each one, (for example " I feel miserable and sad. "). Response options for each question range from 0 to 3 and ask patients about their agreement with the statements or how often they apply

(for example " yes, definitely; yes, sometimes; No, not much; No, not at all "). Scores range from 0 (no anxiety or depression) to 21. Scores ≥ 11 indicate a probable clinical diagnosis of anxiety or depression. A value on the HAD score of 7 or less was taken as normal, scores 8–10 are indicating possible abnormality [15].

Statistical analysis was done using the SPSS program version 20.0. Quantitative data were presented as mean and standard deviation while other non-quantitative data as sex and geographical distribution was presented as number and percentage. Chi-square test was used for categorical data. Pearson correlation was used to measure the association between anxiety and depression scores and the other variables in the three study groups; with (r) is the correlation coefficient. Statistical significance was considered at P- Value ≤ 0.05 .

Results:

This study included four hundred and twenty (420) subjects, 300 patients with chronic obstructive airway who were equally divided according to their diagnosis to group (1) asthma and group (2) COPD. The other 120 subject had no respiratory symptoms and were included in this study as a control group. The demographic data were shown in table 1 for all studied groups. The mean age of the three groups was 34.52 ± 9.53 , 50.3 ± 13 and 33.96 ± 10.695 respectively. The study included 148 females (77 in asthma group, 38 in the COPD group and 33 in control group) and 272 males (73 in asthma group, 112 in COPD group and 87 in control group). All patients in COPD group were smokers with smoking index $415. \pm 311.85$. In asthma patients, there were 42 smokers with smoking index 75.25 ± 126.66 , while in control group, there were 30 smokers with smoking index 96.25 ± 178.32 (table 1).

Regarding pulmonary functions, FEV1 was nearly equal in asthma and COPD (76.36 ± 14.58 , 76.6 ± 18.8), but it was significantly higher in the control group (85.18 ± 15.1), P value 0.0008. COPD group shows more airway obstruction (FEV1/FVC was 68.82 ± 4.95) than asthma group (FEV1/FVC was 77.2 ± 12.82). As regards to small airway functions, it was affected more in asthma group than COPD group (EFE25-75% were 62.56 ± 17.9 and 73.4 ± 21.17) in asthma and COPD respectively p 0.0007. The number of exacerbation per year and duration of illness were matched in asthma and COPD groups, table 1.

Table 1: Descriptive data of the study groups

Variables	Group1 (asthma) No: 150	Group2 (COPD) No: 150	Group3 (control) No: 120
Age	34.52 ± 9.53	50.3 ± 13	33.96 ± 10.695
Sex: Males	73 (48.7%)	112 (74.7%)	87 (72.5%)
Females	77 (51.3%)	38 (25.3%)	33 (27.5%)
Smoking status: Smoker	42	150	30
Non-smoker	108	0	90
Smoking index	75.25 ± 126.66	$415. \pm 311.85$	96.25 ± 178.32
Geographic area			
Riyadh	50 (33.3%)	50 (33.3%)	40 (33.3%)
Jeddah	50 (33.3%)	50 (33.3%)	40 (33.3%)
Khobar	50 (33.3%)	50 (33.3%)	40 (33.3%)
FEV1%	76.36 ± 14.58	76.6 ± 18.8	85.18 ± 15.1
FEV1/FVC	77.2 ± 12.82	68.82 ± 4.95	86.53 ± 7

EFE25-75%	62.56 ± 17.9	73.4 ± 21.17	78.5 ± 29
Anxiety score	8.94± 3.37	6.98±3.15	6.25± 3.03
Depression score	7.12±3.12	5.94± 2.99	4.72 ± 2.52
Number of exacerbation per year	1.76 ± 1.15	2.01 ± 1.19	
Duration of illness in years	13.76 ± 7.2	14.43 ± 9.14	

The anxiety score was higher in asthma group than COPD group and control (8.94±3.37 compared to (6.98±3.15 and 6.25± 3.03) respectively p value (0.0002). For depression, still asthma patients have higher scores than COPD patients (7.12±3.12 and 5.94± 2.99) and both have higher scores than the control group 4.72 ± 2.52, but P value > 0.05. Within the individual group, the anxiety score was higher than depression score.

As regarding geographical distribution of the study groups, the number of cases from each area was predetermined and fixed equal number in each locality (50 patients from each locality for each group and 40 subjects for control from each locality).

Table 2 shows the number and percentage of cases with psychiatric illness. The number of anxiety cases (anxiety score ≥ 11) was higher in asthmatics [42 patients (28%)] than in COPD [33 patients (22%)] while control group had 20 cases (16.7%) with anxiety score ≥ 11. For borderline cases, there were 45 (30 %), 15 (10%), 9 (10%) cases respectively, (P value .9). regarding Depression the number of cases was higher in asthmatics [30 cases (20%)] than COPD [21 cases (14%), both were higher than control [6 cases (5%)], borderline cases were higher in asthmatics [36(24%)] than COPD and control [18 (12%),14 (11.67%)] respectively, p value .05.

In the asthmatic group, both borderline and Anxiety diseases were more common in females than males with highly significant p value (p 0.002). On the other hand, depression was significantly higher in males than females with highly significant statistical differences (p 0.001). In COPD group, anxiety and depression were more prevalent in males (p .004, .11). There were no statistically significant differences in control group between males and females, Table 3.

Table 2: Anxiety and Depression in the study groups

Variables	Group1 (asthma) No: 150	Group2 (COPD) No: 150	Group3 (control) No: 120	p-value
Anxiety				0.9
• No anxiety	63 (42%)	102 (68%)	91 (75.8%)	
• Border line	45 (30%)	15 (10%)	9 (7.5%)	
• diseased	42 (28%)	33 (22%)	20 (16.7%)	
Depression				.05
• No depression	84 (56%)	111 (74%)	100 (83.33%)	
• Border line	36 (24%)	18 (12%)	14 (11.67%)	
• Diseased	30 (20%)	21 (14%)	6 (5%)	
Total	150	150	120	

Table 3: Distribution of psychiatric disorders among males and females

Variables	Asthma	COPD	Control
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	No=150		No=150		No=120	
	Male	female	male	female	male	female
• No anxiety	40	23	75	27	66	25
• Borderline	21	24	7	8	6	3
• Diseased	12	30	30	3	15	5
P-value	.002		.004		.87	
	NO=150		NO=150		NO=120	
	Male	female	male	female	male	female
• No depression	72	12	79	32	72	28
• Borderline	18	18	17	1	9	5
• Diseased	24	6	16	5	6	
P-value	.001		.11		.25	

As table 4 shows, anxiety had a weak negative correlation with age, smoking index, FEV1%, FEV1/FVC% and FEF25-75, while it was weakly correlated positively with number of exacerbation per year and duration of illness in (asthmatics) group 1. Regarding depression, it had also a weak negative correlation with age, smoking index, FEV1/FVC%, and number of exacerbation per year and duration of illness, while it was positively correlated with the other variables. Regarding (COPD) group 2, It was found that anxiety and depression have strong negative correlation with FEV1%, FEV1/FVC% and FEF25-75% while strongly correlated positively with the age, smoking index, the number of exacerbation per year and duration of disease. Regarding control group, there were weak positive and negative correlations between anxiety and depression and other variables except age.

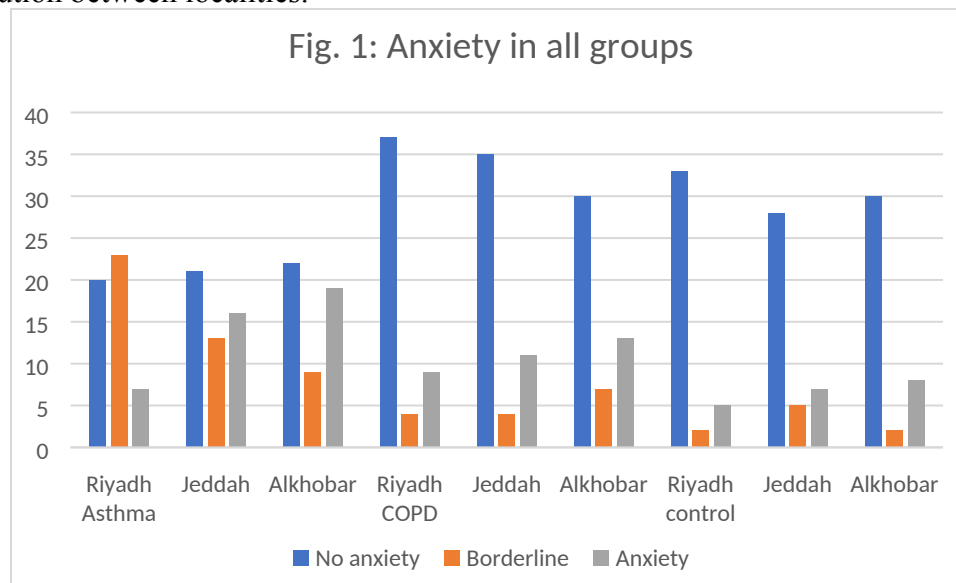
Table 4: Correlations of anxiety and depression in the study group

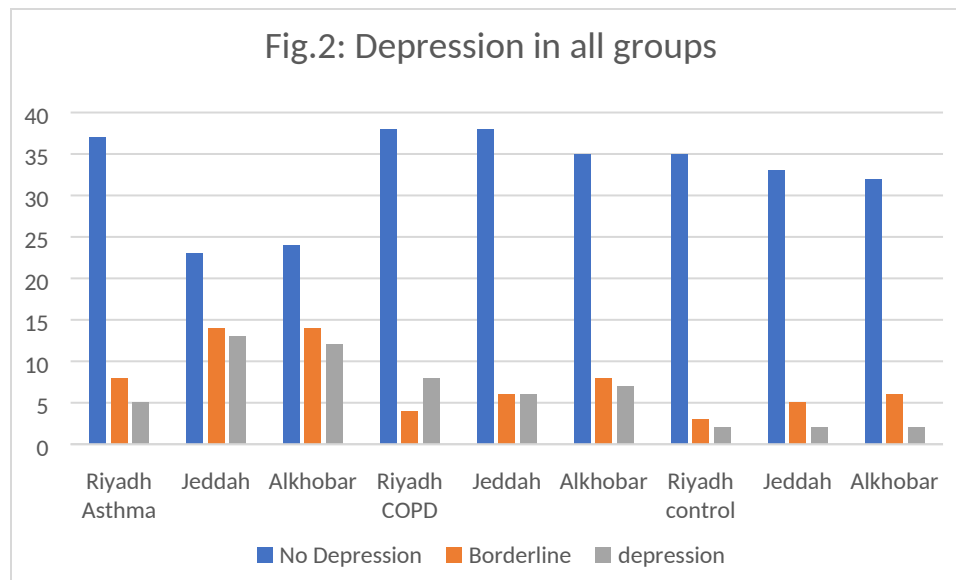
Variables	Asthma				COPD				control			
	Anxiety		Depression		Anxiety		Depression		Anxiety		Depression	
	r	P	r	p	r	p	r	p	r	p	r	p
Age	-.08	.3	-.18	.02	.46	.001	.48	.001	-.2	.8	.04	.65
Smoking index	-.16	.05	-.15	.7	.7	.001	.6	.001	.14	.1	.13	.14
FEV1%	-.01	.9	.23	.004	-.66	.001	-.57	.001	.12	.2	.002	.9
FEV1/FVC%	-.18	.03	-.22	.006	-.48	.001	-.5	.001	.38	.001	.24	.009
FEF25-75%	-.26	.002	.07	.4	-.68	.001	-.6	.001	.31	.001	.22	.018
Number of exacerbation per year	.11	.17	-.04	.065	.7	.001	.68	.001				
Duration of illness	.02	.8	-.29	.000	.6	.001	.57	.001				

Table 5: Anxiety and depression in different localities in the study groups

	Asthma			COPD			control		
	Riyadh	Jeddah	Alkhobar	Riyadh	Jeddah	Alkhobar	Riyadh	Jeddah	Alkhobar
No anxiety	20	21	22	37	35	30	33	28	30
Borderline	23	13	9	4	4	7	2	5	2
Anxiety	7	16	19	9	11	13	5	7	8
P value	.01			.6			.5		
No Depression	37	23	24	38	38	35	35	33	32
Borderline	8	14	14	4	6	8	3	5	6
Depression	5	13	12	8	6	7	2	2	2
P value	.04			.8			.9		

Table 5 showed the number of cases of psychiatric disorders in middle, western and eastern cities in KSA (Riyadh, Jeddah and AL Khobar). There was increased prevalence of anxiety in Al Khobar and Jeddah more than Riyadh for asthmatic patients with a significant statistical difference (P value, .01). For depression, it was higher in Jeddah and AlKobar in asthmatic group with a significant statistical difference (P value, .04). In both COPD and control groups there was no significant difference in distribution between localities.





Discussion:

It is well documented that respiratory and psychological symptoms can be interrelated [16]. Asthma remains one of the most frequently documented chronic respiratory disorders that can be properly controlled [17]. COPD is considered as a systemic disease with multiple co morbidities. Anxiety and depression are considered two of the most common and least-treated comorbidities associated with asthma and COPD. Limited studies had been addressed to inform how to diagnose and manage these disorders and determine their impact on health status among respiratory patients [18].

The current study aimed to evaluate the prevalence of anxiety and depression disorders in asthma and COPD patients in different localities in Saudi Arabia. Also, it aimed to give more awareness about these disorders as regards to information about symptoms presentations. The results of current study showed that the mean ages of asthma group were matched with the control group 34.52 ± 9.53 and 33.96 ± 10.695 respectively. The mean age of COPD group was 50.3 ± 13 , not matching the other groups. Both age and male gender are important independent risk factors for COPD [12]. Chronic obstructive pulmonary disease is prevalent in societies where cigarette smoking is common [19]. It was found that prevalence of anxiety and depression was higher in asthma and COPD groups (28%, 22% for anxiety and 20%, 14% for depression) in comparison to normal population in control group (16.7% and 5%). Both asthma and COPD are chronic inflammatory diseases. The association between depression, anxiety and inflammation has been shown to be bidirectional. Depression enhances inflammation and in turn, inflammation promotes depression. Some stressful situations are more potent than others. Furthermore, it is possible that situations of psychological coping and interpersonal relationships may reduce the impact of stress inflammatory mechanisms [20]. Depression has been characterized as a dysfunction in both the suppression and activation of the immune system [21]. Both anxiety and depression are prevalent in asthma and COPD patients and were positively correlated with an increased number of exacerbations. These results were in agreement with many previous studies in different localities [22-25]. In the current study, results show more prevalence of anxiety and depression in asthma group than COPD group. Carvalho et al reported that anxiety was more prevalent in asthmatics [26]. On the other hand, more recently, *Asnaashari et al.*,

2012 demonstrated that there was no significant difference between asthmatics and COPD patients in terms of general psychopathology, depression or anxiety [27]. Dursun et al., 2015 found similar degrees of anxiety in asthmatic and COPD [28], despite depression was more common in COPD patients. Taghreed et al 2012 found higher depression and anxiety in COPD compared to asthma [25]. This can be explained by different localities between her study and the current study with different climate change and socio economic status. In the present study, anxiety was more common in females than males in asthma group while in COPD and control groups it was more common in males. These results were in agreement to Sundberg et al., study 2009 where he reports that women with asthma had more anxiety than men [29]. A survey by McLean et al., 2011 on 20,013 persons found that women have consistently higher prevalence rates of anxiety disorders than males [30]. In the present study, males have higher rate of depression in all groups (asthma, COPD and control groups). This is in contrary to a study by Marco et al., 2006 in which depression was more common in females than males, and female patients report a higher level of dyspnea than males for the same level of ventilatory impairment [31]. In Dursun Et al., 2015 study, gender has no correlation to anxiety or depression [28].

In the present study, there was weak correlation between anxiety and depression with other variables of pulmonary function in asthmatic patients. This coincides with Krommydas et al., 2004 study where there was no significant difference in FEV1, FEV1/FVC in the asthmatic patients with and without anxiety, however in the same study, there was a difference in those parameters in patients with or without depression [32]. The current results come in agreement with Ryu et al, 2010 study [33]. In the present study, it was found that anxiety and depression in COPD group have strong negative correlation with FEV1%, FEV1/FVC% and FEF25-75% while strongly correlated positively with the age and smoking. Ryu et al., 2010 found that post-bronchodilator FEV1 and smoking history were independent risk factors for depression in patients with chronic airway diseases irrespective of individual diagnosis [33]. In Bratek et al., study 2015, FEV1 was negatively correlated with anxiety, depression and cognitive impairment scores, i.e. more severe airway obstruction was associated with worse psycho-emotional and cognitive functioning [34]. Smoking, inflammation and hypoxia have potential impact on the prevalence of depression in COPD [8].

The results showed increased prevalence of anxiety and depression more in AL Khobar and Jeddah than Riyadh for asthmatic patients with a significant statistical difference. These findings may be related to different climate status and sociocultural behavior between three places. In COPD and control groups there were non-significant statistical changes. These geographical differences may be related to nature of work with its stress and environmental factors.

Conclusion: Psychological problems such as anxiety and depression are important comorbidities associated with respiratory diseases. They occur more commonly in people with asthma and COPD, and are associated with poor outcomes of both diseases. The mechanisms underlying it are still uncertain. females have higher rate of anxiety depression asthma group while in COPD group, psychological problems are more common in males than females. HADS is a simple questionnaire which was accepted by patients and a reliable method to assess anxiety and depression in patients with asthma

and COPD. There is geographical affection of the distribution of psychological problems in KSA. Al Khobar and Jeddah showed more anxiety in both asthma and COPD groups.

Recommendations: Psychiatric health status should be evaluated in patients with chronic respiratory diseases specially asthma and COPD.

Limitations of study: Relative less females in COPD and control groups, and no investigation for patients during exacerbations. Further studies are needed to investigate other localities in KSA as southern areas.

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Prevalence of anxiety and depression in patients with airway obstruction using Hospital Anxiety and Depression Scale (HADS) in different localities of Saudi Arabia

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Short title: Anxiety, depression in asthma and COPD

Summary at a Glance: This study included 420 subjects divided into three groups: Group I asthmatic (150) patients, group II COPD patients (150) and control group contain (120) healthy subjects. All patients and healthy subjects were instructed to answer the questionnaire of HADS. Anxiety and depression scales were calculated with prevalence of each. Anxiety and depression were more common in people with asthma and COPD.

Abstract:

Background: Both of asthma and COPD affect psychological state due to their impact on general activities of patients and their ability to cause anxiety and depression. The Hospital Anxiety and Depression Scale, HADS, was designed to provide a simple and reliable tool for use in medical practice. **Aim:** This study aimed to evaluate the prevalence of anxiety and depression disorders in asthma and COPD patients in different Saudi Arabia localities and their relationship to pulmonary function. **Patients and methods:** This study included 420 subjects from three different places in KSA (Jeddah, Riyadh and AL Khobar) and were divided into three groups. Group I asthmatic patients included (150) patients, group II COPD patients included (150) patients and control group contain (120) healthy subjects. All patients were instructed to answer the questionnaire of HADS.

Results: There is increased prevalence of anxiety and depression in both asthma (28%, 20%) and COPD (22%, 14%) patients in comparison to control group (16%, 4%) respectively. Anxiety was more common in females than males in asthmatics with highly significant statistical differences ($p = 0.002$) while depression was common in males than females with highly significant statistical differences ($p = 0.001$). In COPD group, anxiety and depression were more prevalent in males with highly significant statistical differences for anxiety between males and females ($p = 0.004$) and non-significant differences for depression. In (COPD) group, it was found that anxiety and depression have strong negative correlation with pulmonary function and strong positive correlation with the age, smoking index, number of exacerbations per year and duration of disease while in asthma and control groups the correlations were weak. Geographically, Anxiety and depression were more in AL-Khobar and Jeddah than Riyadh in asthmatic patients ($P=0.01, .04$) while no significant difference in geographical distribution in COPD and control.

Conclusions: Asthma and COPD patients are prone to anxiety and depression more than normal populations, this lead to poor outcomes of both diseases.

Keywords: Asthma, COPD, anxiety, depression, HADS

Background:

Patients with asthma and chronic obstructive pulmonary disease represent the majority of patients attending pulmonary outpatient clinics and also attending frequently the primary care clinics. Asthma is an inflammatory disorder of the airways that many inflammatory cells and multiple mediators that result in characteristic pathophysiological changes take apart. Asthma is characterized by persistent airway inflammation with episodic symptoms [1]. Chronic Obstructive Pulmonary Disease (COPD) is a common preventable and treatable disease. It is characterized by progressive persistent airflow limitation [2]. A concurrent psychiatric disorder including anxiety and depression may complicate the quality of life of a chronically airway obstructed patients. This may bring the patient into a vicious circle of affecting each other's [3]. On the other hand, studies show that psychiatric wellness can improve lung function response and pulmonary health [4,5]. Studies had shown that patients with asthma have double risk of developing depressive symptoms as compared with those who do not have asthma [6]. There is a controversy between asthma severity and presence of anxiety and depression despite their association [7]. Anxiety and depression are also well-recognized major comorbidities in Chronic Obstructive Pulmonary Disease [8]. It is well known that, psychiatric conditions are not regularly diagnosed in respiratory patients and are not well treated [5,9]. The awareness of the presence and severity of psychiatric disorders in patients with chronic respiratory conditions encourages patients to take the necessary measures for treatment. Psychiatric problems negatively influence disease severity and quality of life of the patients.

The Hospital Anxiety and Depression Scale, or HADS, was designed to provide a simple and reliable tool for use in medical practice.]. It was evaluated by local psychiatric group and was validated to be applied for pulmonary outpatient attendances. It is valid to be used in a hospital setting as well as in community settings and in primary care medical practice [10]

Aim of the study:

This study aimed to evaluate the prevalence of anxiety and depression disorders in asthma and COPD patients in three different Saudi Arabia localities and their correlation to pulmonary function test. Also, it aimed to give more awareness about these disorders as regards symptoms and appropriate management.

Patients and methods:

Patients: this study included four hundred twenty (420) subjects divided into three groups. Group I controlled asthmatic patients (150) patients, group II stable COPD (150) patients and control group (120) healthy subjects. They were equally distributed between three localities (Riyadh, Jeddah, ALKhobar). The inclusion criteria included, stable asthma patients, stable COPD patients older than 18 years old and patient signing a written consent for the study. Exclusion criteria included other chronic diseases, any previously diagnosed psychiatric problems, disturbed conscious level and refusal to sign the consent. Study was approved from local ethics committee.

Methods: (300) patients were recruited from pulmonary outpatient clinic from three different places in KSA (Jeddah, Riyadh and AL Khobar) during the period between October 2015 and October 2016. One hundred twenty (120) volunteer subjects were included in this study as a control group. Fifty asthmatic patients, fifty COPD patient s and forty healthy control subjects were investigated in each locality. Informed written

consent was obtained from each subject after explaining the purpose of the study to him/her.

All the three groups underwent full history taking including history of smoking (current, ex, and non-smoking), history of chest symptoms (cough, expectoration, wheezes and dyspnea), and number of exacerbation in the last year and history of any other co morbidities. Also, thorough clinical examination, general and local respiratory system examination was done. The average number of exacerbation per year and duration of illness was calculated in the previous 5 years and average was taken.

Physiological assessment was also done using spirometry. Flow/volume loop was performed to all cases. The test was done before and 20 min. after 2 puffs of Salbutamol (200 µg) via a metered dose inhaler (COPD was diagnosed as fixed, non-reversible airflow limitation with change < 12% post bronchodilator). All data were expressed in percent of predicted value (FEV1%, FVC%, FEV1/FVC%). Diagnosis of asthma was made depending on clinical picture and examination. According to GINA 2015 [11], controlled asthma was defined as the need for rescue medications twice or less a week (short-acting b2-agonists), no limitation of daily activity, no nocturnal symptoms, twice or less a week, daytime symptoms, and forced expiratory volume in the first second (FEV1)% greater than 80% predicted. There were no exacerbations (needing hospital admission or ER visit). On the other hand, diagnosis of COPD was relayed on GOLD criteria for COPD diagnosis according to results of spirometry [12], also patients were stable not in exacerbation or need for hospital admission or ER visit.

Hospital Anxiety and Depression Scale (HADS): All patients had completed the questionnaire of German version of the hospital anxiety and depression scale [13,14]. It measures anxiety and depression in outpatient settings. It contains 14 statements describing symptoms of anxiety and depression, seven statements for each one, (for example " I feel miserable and sad. "). Response options for each question range from 0 to 3 and ask patients about their agreement with the statements or how often they apply (for example " yes, definitely; yes, sometimes; No, not much; No, not at all "). Scores range from 0 (no anxiety or depression) to 21. Scores ≥ 11 indicate a probable clinical diagnosis of anxiety or depression. A value on the HAD score of 7 or less was taken as normal, scores 8–10 are indicating possible abnormality [15].

Statistical analysis was done using the SPSS program version 20.0. Quantitative data were presented as mean and standard deviation while other non-quantitative data as sex and geographical distribution was presented as number and percentage. Chi-square test was used for categorical data. Pearson correlation was used to measure the association between anxiety and depression scores and the other variables in the three study groups; with (r) is the correlation coefficient. Statistical significance was considered at P- Value ≤ 0.05 .

Results:

This study included four hundred and twenty (420) subjects, 300 patients with chronic obstructive airway who were equally divided according to their diagnosis to group (1) asthma and group (2) COPD. The other 120 subject had no respiratory symptoms and were included in this study as a control group. The demographic data were shown in table 1 for all studied groups. The mean age of the three groups was 34.52 ± 9.53 , 50.3 ± 13 and 33.96 ± 10.695 respectively. The study included 148 females (77 in asthma group, 38 in the COPD group and 33 in control group) and 272 males (73 in

asthma group, 112 in COPD group and 87 in control group). All patients in COPD group were smokers with smoking index $415. \pm 311.85$. In asthma patients, there were 42 smokers with smoking index 75.25 ± 126.66 , while in control group, there were 30 smokers with smoking index 96.25 ± 178.32 (table 1).

Regarding pulmonary functions, FEV1 was nearly equal in asthma and COPD (76.36 ± 14.58 , 76.6 ± 18.8), but it was significantly higher in the control group (85.18 ± 15.1), P value 0.0008. COPD group shows more airway obstruction (FEV1/FVC was 68.82 ± 4.95) than asthma group (FEV1/FVC was 77.2 ± 12.82). As regards to small airway functions, it was affected more in asthma group than COPD group (EFE25-75% were 62.56 ± 17.9 and 73.4 ± 21.17) in asthma and COPD respectively p 0.0007. The number of exacerbation per year and duration of illness were matched in asthma and COPD groups, table 1.

Table 1: Descriptive data of the study groups

Variables	Group1 (asthma) No: 50	Group2 (COPD) No: 50	Group3 (control) No: 50
Age	34.52 ± 9.53	50.3 ± 13	33.96 ± 10.695
Sex: Males	73 (48.7%)	112 (74.7%)	87 (72.5%)
Females	77 (51.3%)	38 (25.3%)	33 (27.5%)
Smoking status: Smoker	42	150	30
Non-smoker	108	0	90
Smoking index	75.25 ± 126.66	$415. \pm 311.85$	96.25 ± 178.32
Geographic area			
Riyadh	50 (33.3%)	50 (33.3%)	40 (33.3%)
Jeddah	50 (33.3%)	50 (33.3%)	40 (33.3%)
Khobar	50 (33.3%)	50 (33.3%)	40 (33.3%)
FEV1%	76.36 ± 14.58	76.6 ± 18.8	85.18 ± 15.1
FEV1/FVC	77.2 ± 12.82	68.82 ± 4.95	86.53 ± 7
EFE25-75%	62.56 ± 17.9	73.4 ± 21.17	78.5 ± 29
Anxiety score	8.94 ± 3.37	6.98 ± 3.15	6.25 ± 3.03
Depression score	7.12 ± 3.12	5.94 ± 2.99	4.72 ± 2.52
Number of exacerbation per year	1.76 ± 1.15	2.01 ± 1.19	
Duration of illness in years	13.76 ± 7.2	14.43 ± 9.14	

The anxiety score was higher in asthma group than COPD group and control (8.94 ± 3.37 compared to (6.98 ± 3.15 and 6.25 ± 3.03) respectively p value (0.0002). For depression, still asthma patients have higher scores than COPD patients (7.12 ± 3.12 and 5.94 ± 2.99) and both have higher scores than the control group 4.72 ± 2.52 , but P value > 0.05. Within the individual group, the anxiety score was higher than depression score.

As regarding geographical distribution of the study groups, the number of cases from each area was predetermined and fixed equal number in each locality (50 patients from each locality for each group and 40 subjects for control from each locality).

Table 2 shows the number and percentage of cases with psychiatric illness. The number of anxiety cases (anxiety score ≥ 11) was higher in asthmatics [42 patients (28%)] than in COPD [33 patients (22%)] while control group had 20 cases (16.7%) with anxiety score ≥ 11 . For borderline cases, there were 45 (30 %), 15 (10%), 9 (10%) cases

respectively, (P value .9). regarding Depression the number of cases was higher in asthmatics [30 cases (20%)] than COPD [21 cases (14%), both were higher than control [6 cases (5%)], borderline cases were higher in asthmatics [36(24%)] than COPD and control [18 (12%),14 (11.67%)] respectively, p value .05.

In the asthmatic group, both borderline and Anxiety diseases were more common in females than males with highly significant p value (p 0.002). On the other hand, depression was significantly higher in males than females with highly significant statistical differences (p 0.001). In COPD group, anxiety and depression were more prevalent in males (p .004, .11). There were no statistically significant differences in control group between males and females, Table 3.

Table 2: Anxiety and Depression in the study groups

Variables	Group1 (asthma) No: 150	Group2 (COPD) No: 150	Group3 (control) No: 120	p-value
Anxiety				0.9
• No anxiety	63 (42%)	102 (68%)	91 (75.8%)	
• Border line	45 (30%)	15 (10%)	9 (7.5%)	
• diseased	42 (28%)	33 (22%)	20 (16.7%)	
Depression				.05
• No depression	84 (56%)	111 (74%)	100 (83.33%)	
• Border line	36 (24%)	18 (12%)	14 (11.67%)	
• Diseased	30 (20%)	21 (14%)	6 (5%)	
Total	150	150	120	

Table 3: Distribution of psychiatric disorders among males and females

Variables	Asthma		COPD		Control	
	No=150		No=150		No=120	
	Male	female	male	female	male	female
• No anxiety	40	23	75	27	66	25
• Borderline	21	24	7	8	6	3
• Diseased	12	30	30	3	15	5
P-value	.002		.004		.87	
	NO=150		NO=150		NO=120	
	Male	female	male	female	male	female
• No depression	72	12	79	32	72	28
• Borderline	18	18	17	1	9	5
• Diseased	24	6	16	5	6	
P-value	.001		.11		.25	

As table 4 shows, anxiety had a weak negative correlation with age, smoking index, FEV1%, FEV1/FVC% and FEF25-75, while it was weakly correlated positively with number of exacerbation per year and duration of illness in (asthmatics) group 1. Regarding depression, it had also a weak negative correlation with age, smoking index, FEV1/FVC%, and number of exacerbation per year and duration of illness, while it was positively correlated with the other variables. Regarding (COPD) group 2, It was found

that anxiety and depression have strong negative correlation with FEV1%, FEV1/FVC% and FEF25-75% while strongly correlated positively with the age, smoking index, the number of exacerbation per year and duration of disease. Regarding control group, there were weak positive and negative correlations between anxiety and depression and other variables except age.

Table 4: Correlations of anxiety and depression in the study group

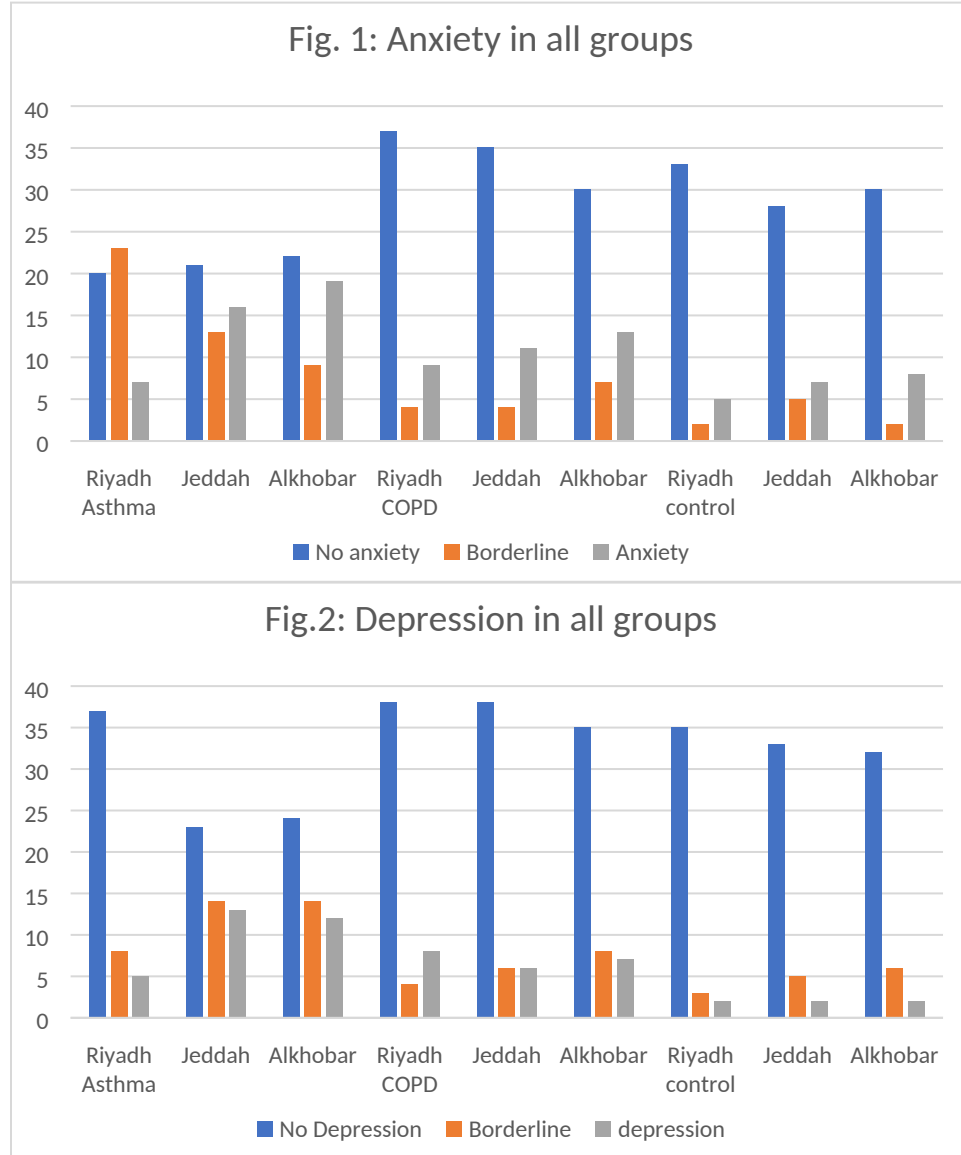
Variables	Asthma				COPD				control			
	Anxiety		Depression		Anxiety		Depression		Anxiety		Depression	
	r	P	r	p	r	p	r	p	r	p	r	p
Age	-.08	.3	-.18	.02	.46	.001	.48	.001	-.2	.8	.04	.65
Smoking index	-.16	.05	-.15	.7	.7	.001	.6	.001	.14	.1	.13	.14
FEV1%	-.01	.9	.23	.004	-.66	.001	-.57	.001	.12	.2	.002	.9
FEV1/FVC%	-.18	.03	-.22	.006	-.48	.001	-.5	.001	.38	.001	.24	.009
FEF25-75%	-.26	.002	.07	.4	-.68	.001	-.6	.001	.31	.001	.22	.018
Number of exacerbation per year	.11	.17	-.04	.065	.7	.001	.68	.001				
Duration of illness	.02	.8	-.29	.000	.6	.001	.57	.001				

Table 5: Anxiety and depression in different localities in the study groups

	Asthma			COPD			control		
	Riyadh	Jeddah	Alkhobar	Riyadh	Jeddah	Alkhobar	Riyadh	Jeddah	Alkhobar
No anxiety	20	21	22	37	35	30	33	28	30
Borderline	23	13	9	4	4	7	2	5	2
Anxiety	7	16	19	9	11	13	5	7	8
P value	.01			.6			.5		
No Depression	37	23	24	38	38	35	35	33	32
Borderline	8	14	14	4	6	8	3	5	6
Depression	5	13	12	8	6	7	2	2	2
P value	.04			.8			.9		

Table 5 showed the number of cases of psychiatric disorders in middle, western and eastern cities in KSA (Riyadh, Jeddah and AL Khobar). There was increased prevalence of anxiety in Al Khobar and Jeddah more than Riyadh for asthmatic patients with a significant statistical difference (P value, .01). For depression, it was higher in Jeddah and AlKobar in asthmatic group with a significant statistical difference (P

value, .04). In both COPD and control groups there was no significant difference in distribution between localities.



Discussion:

It is well documented that respiratory and psychological symptoms can be interrelated [16]. Asthma remains one of the most frequently documented chronic respiratory disorders that can be properly controlled [17]. COPD is considered as a systemic disease with multiple co morbidities. Anxiety and depression are considered two of the most common and least-treated comorbidities associated with asthma and COPD. Limited studies had been addressed to inform how to diagnose and manage these disorders and determine their impact on health status among respiratory patients [18].

The current study aimed to evaluate the prevalence of anxiety and depression disorders in asthma and COPD patients in different localities in Saudi Arabia. Also, it aimed to give more awareness about these disorders as regards to information about symptoms presentations. The results of current study showed that the mean ages of asthma group were matched with the control group 34.52 ± 9.53 and 33.96 ± 10.695

respectively. The mean age of COPD group was 50.3 ± 13 , not matching the other groups. Both age and male gender are important independent risk factors for COPD [12]. Chronic obstructive pulmonary disease is prevalent in societies where cigarette smoking is common [19]. It was found that prevalence of anxiety and depression was higher in asthma and COPD groups (28%, 22% for anxiety and 20%, 14% for depression) in comparison to normal population in control group (16.7% and 5%). Both asthma and COPD are chronic inflammatory diseases. The association between depression, anxiety and inflammation has been shown to be bidirectional. Depression enhances inflammation and in turn, inflammation promotes depression. Some stressful situations are more potent than others. Furthermore, it is possible that situations of psychological coping and interpersonal relationships may reduce the impact of stress inflammatory mechanisms [20]. Depression has been characterized as a dysfunction in both the suppression and activation of the immune system [21]. Both anxiety and depression are prevalent in asthma and COPD patients and were positively correlated with an increased number of exacerbations. These results were in agreement with many previous studies in different localities [22-25]. In the current study, results show more prevalence of anxiety and depression in asthma group than COPD group. Carvalho et al reported that anxiety was more prevalent in asthmatics [26]. On the other hand, more recently, *Asnaashari et al.*, 2012 demonstrated that there was no significant difference between asthmatics and COPD patients in terms of general psychopathology, depression or anxiety [27]. Dursun et al., 2015 found similar degrees of anxiety in asthmatic and COPD [28], despite depression was more common in COPD patients. Taghreed et al 2012 found higher depression and anxiety in COPD compared to asthma [25]. This can be explained by different localities between her study and the current study with different climate change and socio economic status. In the present study, anxiety was more common in females than males in asthma group while in COPD and control groups it was more common in males. These results were in agreement to Sundberg et al., study 2009 where he reports that women with asthma had more anxiety than men [29]. A survey by McLean et al., 2011 on 20,013 persons found that women have consistently higher prevalence rates of anxiety disorders than males [30]. In the present study, males have higher rate of depression in all groups (asthma, COPD and control groups). This is in contrary to a study by Marco et al., 2006 in which depression was more common in females than males, and female patients report a higher level of dyspnea than males for the same level of ventilatory impairment [31]. In Dursun Et al., 2015 study, gender has no correlation to anxiety or depression [28].

In the present study, there was weak correlation between anxiety and depression with other variables of pulmonary function in asthmatic patients. This coincides with Krommydas et al., 2004 study where there was no significant difference in FEV1, FEV1/FVC in the asthmatic patients with and without anxiety, however in the same study, there was a difference in those parameters in patients with or without depression [32]. The current results come in agreement with Ryu et al, 2010 study [33]. In the present study, it was found that anxiety and depression in COPD group have strong negative correlation with FEV1%, FEV1/FVC% and FEF25-75% while strongly correlated positively with the age and smoking. Ryu et al., 2010 found that post-bronchodilator FEV1 and smoking history were independent risk factors for depression in patients with chronic airway diseases irrespective of individual diagnosis [33]. In Bratek

et al., study 2015, FEV1 was negatively correlated with anxiety, depression and cognitive impairment scores, i.e. more severe airway obstruction was associated with worse psycho-emotional and cognitive functioning [34]. Smoking, inflammation and hypoxia have potential impact on the prevalence of depression in COPD [8].

The results showed increased prevalence of anxiety and depression more in AL Khobar and Jeddah than Riyadh for asthmatic patients with a significant statistical difference. These findings may be related to different climate status and sociocultural behavior between three places. In COPD and control groups there were non-significant statistical changes. These geographical differences may be related to nature of work with its stress and environmental factors.

Conclusion: Psychological problems such as anxiety and depression are important comorbidities associated with respiratory diseases. They occur more commonly in people with asthma and COPD, and are associated with poor outcomes of both diseases. The mechanisms underlying it are still uncertain. females have higher rate of anxiety depression asthma group while in COPD group, psychological problems are more common in males than females. HADS is a simple questionnaire which was accepted by patients and a reliable method to assess anxiety and depression in patients with asthma and COPD. There is geographical affection of the distribution of psychological problems in KSA. Al Khobar and Jeddah showed more anxiety in both asthma and COPD groups.

Recommendations: Psychiatric health status should be evaluated in patients with chronic respiratory diseases specially asthma and COPD.

Limitations of study: Relative less females in COPD and control groups, and no investigation for patients during exacerbations. Further studies are needed to investigate other localities in KSA as southern areas.

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Rebuttal to reviewer's comments

- what are the criteria for diagnosis of COPD & Asthma

already done and added in patients and methods

- What is the reference for HADS

15

- Attach the HADS questionnaire to the appendix

Added as supplementary file

- In table 1 headings you wrote the number of each group is 50 which is wrong.

Already corrected

مقياس القلق Hospital anxiety and depression Scale

1. I feel tense or wound up			1. أشعر بتوتر
• Most of time	3	3	• معظم الأوقات
• A lot of time	2	2	• كثيرا
• From time to time (occasionally)	1	1	• أحيانا
• Not at all	0	0	• لا أبدا

2. I get a sort of frightened feeling as if something awful is about to happen			2. أشعر بنوع من التخوف كما لو كان شيئا مزعجا سيحدث أو على وشك الحدوث
• Very definitely and quite badly	3	3	• بالطبع وسيء تماما
• Yes, but not too badly	2	2	• نعم وسيء جدا
• A little, but does not worry me	1	1	• بسيط ولا يؤرقني
• Not at all	0	0	• لا أبدا

3. Worrying thoughts go through my mind			3. أفكار من التوجس تدور بفكري
• A great deal of time	3	3	• معظم الأوقات
• A lot of time	2	2	• كثيرا
• From time to time, but not too often	1	1	• من وقت لآخر
• Only occasionally	0	0	• أحيانا

4. I can set at ease and feel relaxed			4. أستطيع الجلوس باسترخاء وأشعر بالراحة
• Definitely	0	0	• دائما
• Usually	1	1	• عادة
• Not often	2	2	• ليس معتادا
• Not at all	3	3	• لا أبدا

5. I get a sort of frightened feeling as butterfly in the stomach			5. أشعر بنوع من التخوف كأن فراشة تقبض على معدتي
• Not at all	0	0	• لا أبدا
• Occasionally	1	1	• أحيانا
• Quite often	2	2	• كثيرا
• Very often	3	3	• كثيرا جدا

6. I feel restless as I have to be on the move			6. أشعر بعدم الراحة كما لو كنت في حركة دائمة
• Very much indeed	3	3	• معظم الأوقات
• Quite a lot	2	2	• كثيرا
• Not very much	1	1	• ليس كثيرا جدا
• Not at all	0	0	• لا أبدا

7. I get sudden feeling of panic			7. أشعر بالهلع المفاجيء (الخوف الشديد)
• Very often indeed	3	3	• عادة بكثرة
• Quite often	2	2	• عادة
• Not very often	1	1	• ليس بعادة جدا
• Not at all	0	0	• لا أبدا

مقياس الاكتئاب

1. I still enjoy the things I used to enjoy			1. لازلت أستمتع بما كان يمتعني من قبل
• Definitely as much	0	0	• بالطبع كثيرا
• Not quit so much	1	1	• ليس كثيرا
• Only little	2	2	• قليلا
• Hardly all	3	3	• لا أبدا

2. I can laugh and see funny side of things			2. أستطيع الضحك ورؤية الجانب الممتع من الأشياء
• As much as I always could	0	0	• كثيرا كلما استطعت
• Not quite so much now	1	1	• ليس تماما في الوقت الحالي
• Definitely not so much now	2	2	• بالطبع ليس كثيرا حاليا
• Not at all	3	3	• لا أبدا

3. I feel cheerful			3. أشعر بالسعادة و السرور
• Not at all	3	3	• لا أبدا
• Not often	2	2	• ليس معتادا
• Sometimes	1	1	• أحيانا
• Most of time	0	0	• معظم الاوقات

4. I feel if I am slowed down			4. أشعر كما لو أنني متباطيء أو كسلان
• Nearly all the time	3	3	• تقريبا كل الوقت
• Very often	2	2	• عادة جدا
• Sometimes	1	1	• أحيانا
• Not at all	0	0	• لا أبدا

5. I have lost interest in my appearance			5. فقدت الاهتمام بمظهري
• Definitely	3	3	• أكيد
• I don not take as much care as I should	2	2	• لا أعطيه الاهتمام المناسب
• I may not take quite as much care	1	1	• ربما أعطيه بعضا من الاهتمام
• I take just as much care as ever	0	0	• ما زلت أعطيه نفس الاهتمام

6. I look forward with enjoyment to things			6. أبحث عن التمتع بالأشياء
• As much as I ever did	0	0	• كلما استطعت أن أفعل
• Rather less than I used to	1	1	• ربما أقل مما اعتدت أن أفعله
• Definitely less than I used to	2	2	• بالطبع أقل مما اعتدت أن أفعله
• Hardly at all	3	3	• لا أبدا

7. I can enjoy a good book, radio or TV program			7. أستطيع الاستمتاع بكتاب جديد أو سماع راديو أو مشاهدة برنامج تليفزيوني
• Often	0	0	• دائما
• Sometimes	1	1	• أحيانا
• Not often	2	2	• ليس دائما
• Very seldom	3	3	• نادرا جدا

Normal= 0-7

Borderline= 8-10

Abnormal=11-21