

## Assessment of Psychological Health Status in Geriatric Patients with Obstructive Sleep Apnea

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### Abstract

**Background:** obstructive sleep apnea is a chronic and highly prevalent disorder that is considered to be a true public health problem. The sleep disturbance pattern related to obstructive sleep apnea negatively influences the stress system and hence increases the vulnerability of obstructive sleep apnea patients to anxiety and depression. Aim: Assess the psychological health status in geriatric patients with obstructive sleep apnea. **Method:** Descriptive research design was used in this study. This study was conducted in the outpatient clinic of the Chest Medicine Department at Main Mansoura University Hospital. A purposive sample of 100 geriatric patients with obstructive sleep apnea was enrolled in the study. Data was collected using 3 tools; Geriatric Patient's Demographic characteristics and Clinical Data Sheet, hospital anxiety and depression scale, and Epworth Sleepiness Scale. **Results:** The mean score of anxiety was  $12.03 \pm 3.76$  and depression was  $9.16 \pm 2.86$  with 80.0% of the studied elders had anxiety and 64.0% had depression. In addition, a strong positive correlation was found between obstructive sleep apnea severity and anxiety and depression ( $P=0.001^*$ ). **Conclusion:** Anxiety and depression were common psychological problems in geriatric patients with obstructive sleep apnea. **Recommendation:** Implementation of an intervention program for nursing staff about problems faced in caring for patients with obstructive sleep apnea to help them to provide optimal care and early screening of psychological problems in order to prevent further deterioration.

**Keywords:** Psychological health Status, Obstructive sleep apnea, Geriatric patients.

## **Introduction**

The aging population of the world is rapidly increasing. The proportion of older adults  $\geq 60$  years old will double from 12% to 22% Between 2015 and 2050. The increase in the aged population will bring with it a huge burden of sleep-related health problems<sup>1</sup>. Particularly, patient with obstructive sleep apnea (OSA) is the most common form of sleep-related breathing disorder. OSA Is characterized by the upper airway's complete or partial occlusion during sleep. The results restrict airflow and can result in intermittent hypoxemia and fragmentation of sleep<sup>2</sup>. Mental health is a significant factor in the health status of older adults and it has significant importance in accomplishing successful aging and having a satisfactory quality of life among older adults in different societies<sup>3</sup>.

The recurrent sleep disturbance caused by untreated OSA has a significant sequel for daytime functioning, consisting of profound daytime somnolence and deterioration in emotional well-being. Psychological symptoms such as depression and anxiety are one of the most common comorbidities in obstructive sleep apnea patients that may affect prognosis, quality of life and adherence to treatments<sup>4</sup>. Hence, the psychological health status of geriatric patients with obstructive sleep apnea should be assessed.

### **Research questions:**

**Q1:** What is the level of psychological health status in geriatric patients with obstructive sleep apnea?

**Q2:** What is a relationship between OSA severity and psychological health status in geriatric patients with obstructive sleep apnea?

## **Method**

**Research design:** Descriptive design was utilize to conduct this study.

### **Study setting :**

This study was carried out in the outpatient clinic of the Chest Medicine Department at Main Mansoura University Hospital.

### **Subjects of the study:**

The study included a purposive sample of 100 elderly patients diagnosed with OSA. Elderly patients were selected according to certain characteristics; patient aged 60 years and more, a patient diagnosed with obstructive sleep apnea, able to interact, ready to participate in the study, and available at the selected setting during the period of data collection. Exclusion criteria included the patients suffering from; neurological disorders, respiratory disorders other than OSA, with a history of traumatic brain injury, taking medication that may affect cerebral functioning, and patients undergoing treatment for OSA. The sample size was estimated through clincal.com sample size calculator software, at 5%  $\alpha$  error (95.0% significance) and 10.0%  $\beta$  error (90.0% power of the study), the average minimal state examination among elderly not suffering from OSA was  $29.6 \pm 0.6$ , while among elderly suffering from OSA was  $29.4 \pm 0.8$ <sup>5</sup>. The calculated sample size was 95 subjects and we could add 5.0% for a better quality of collected data so; the field sample was 100 patients.

### **Tool of data collection:-**

Three tools were used for data collection:

#### **Tool 1: Demographic and clinical data structured interview sheet**

It consists of three parts:

**Part I:** Demographic characteristics of the geriatric patients with obstructive sleep apnea which include age, sex,

marital status, residence, level of education, and occupation.

**Part II:** Medical history of geriatric patients with obstructive sleep apnea such as family history, symptoms of the disease, medical diseases, and medication used.

**Part III:** Clinical data related to disease including body weight, height, body mass index (BMI), Neck circumference, polysomnography data, and obstructive sleep apnea severity.

**Tool 2: Epworth sleepiness scale (ESS)**

The Epworth Sleepiness Scale was developed by **Johns (1991)**<sup>6</sup>. It is a valid instrument used to measure excessive daytime sleepiness. It was translated into Arabic and was approved for validity and reliability by **Ahmed et al (2014)**<sup>7</sup>. The subject self-rates on how likely it is that he/she would doze in 8 different situations. The scoring of the answers is ranged from 0-3, with 0 being "Would never doze" and 3 being "high chance of dozing" The total score ranged from 0 to 24 points. A score higher than 10 is usually used to denotes excessive daytime sleepiness.

**Tool 3: Hospital Anxiety and Depression Scale (HADS)**

It was developed by **Zigmond and Snaith (1983)**<sup>8</sup>. HADS is used to assessing levels of anxiety and depression. It was translated into Arabic and was approved for validity and reliability by **Abd El-Hamid (2010)**<sup>9</sup>. HADS includes statements based on past week experience that the patient rates. The 14 statements involve common anxiety (seven statements) or 'depression' (seven statements), the final being mostly (but not entirely) consisting of reflections of the condition of anaerobia. There are 4 possible answers to each question. Answer choices varied between 3 and 0. Both subscales, anxiety (HADS-

A) and depression (HADS-D) are independent measures. The total score of the scale range from 0-21 point and patients can be categorized as the following: normal from 0–7, mild from 8–10, moderate from 11–15, and severe from 16–21.

**Data collection process:**

1. An official letter was obtained from the Dean of Faculty of Nursing, Mansoura University to the responsible authorities to obtain their approval & cooperation.
2. Tool I (Demographic and Clinical data structured interview schedule) was developed by the researcher based on relevant literature.
3. The Arabic version of tool II (Epworth Sleepiness Scale (ESS) was used by the researcher in this study. The reliability of this scale was assured by means of r coefficient ( $r= 0.87$ ).
4. The Arabic version of tool III (Hospital Anxiety and Depression Scale (HADS) was used by the researcher in this study. The reliability of this scale was assured by means of r coefficient ( $r= 0.81$ ).
5. Study tools (tool I, tool II, and tool III) were tested for content validity by a jury of five experts in the fields of Gerontological Nursing and Medical-Surgical Nursing. Accordingly, their recommended modifications had been done and the final forms were used for data collection.
6. A pilot study was conducted on 10% of the sample size of elderly patients from the same mentioned setting before starting data collection to check and confirm the applicability of the study tools. Based on the pilot study, necessary modification includes clarification,

and rewording these elderly patients were excluded from the study sample and the results of the study.

7. After an explanation of the purpose of the study for each patient who fulfills the study criteria, and obtained a necessary verbal consent. Then, the necessary data were collected using the study tools.
8. According to the schedule of the outpatient clinic of the Chest Medicine Department at Main Mansoura University Hospital, The researcher visited the clinic 3 days per week. The time appropriated to complete the study tools lasted for 30 to 40 minutes.
9. Every geriatric patient was interviewed individually by the researcher to collect the necessary information via all study tools and reviewing patient's records.
10. The researcher started the interview by introducing herself to the eligible geriatric patient, giving a brief idea about the aim and nature of the study. Then the necessary data was taken.
11. Data collection started from the beginning of December 2019 till the end of March 2020.

**Ethical considerations:**

Ethical approval was obtained from Mansoura University, Faculty of Nursing Ethic Committee. Verbal consent was obtained from geriatric patients after explanation of the nature of the study. The participants were informed that their participation is voluntary and they can withdraw from the study at any time. Confidentiality and anonymity of the collected data were assured.

**Statistical analysis:**

The collected data were organized, tabulated and statistically analyzed using SPSS software (Statistical Package for the Social Sciences) version 22. For quantitative data, the range, mean and standard deviation were calculated. For qualitative data, which describe a categorical set of data by frequency, percentage or proportion of each category. ). For comparison between means of two groups of parametric data of independent samples, student t-test was used. For comparison between more than two means of parametric data, F value of ANOVA test was calculated. Correlation between variables was evaluated using Pearson's correlation coefficient (r). Significance was adopted at  $p < 0.05$  for interpretation of results of tests of significance. Regression to detect the most independent/ affecting factor for HAD scale was done.

**Results:**

**Figure 1** shows that 47.0% of the studied patients had a moderate anxiety level, while 20.0% had a normal anxiety level. The total mean score of anxiety level was  $12.03 \pm 3.76$  with a minimum of 5 and a maximum of 20.

**Figure 2** shows that 41.0% of the studied patients had mild depression levels and 23.0% had moderate depression levels. The total mean score of depression level was  $9.16 \pm 2.86$  with a minimum of 2 and a maximum of 15.

**Figure 3** presented that 76.0% of the studied elder patients had excessive daytime sleepiness and only 24.0% had normal daytime sleepiness. The total mean score of daytime sleepiness was  $15.14 \pm 5.86$ .

**Table 1** demonstrates the distribution of the studied elderly patients with obstructive sleep apnea according to their

PSG findings. REM of the studied elderly patients ranged from 0.0 to 74.50 % from total sleep with a mean (REM) of  $9.71 \pm 13.83$ . The light sleep stage ranged from 25.50 to 100.0 % with a mean light sleep of  $86.42 \pm 12.53$  and the deep sleep stage (N3) ranged from 0.0 to 28.70 % with a mean deep sleep of  $5.11 \pm 7.30$ . Regarding the total sleep time (TST) of the studied elderly patients ranged from 2.0 to 6.0 hours with a mean (TST) of  $4.87 \pm 1.08$ .

As regards obstructive sleep apnea severity indicated by Apnea-Hypopnea Index (AHI), it was observed that 78.0% had severe obstructive sleep apnea, 14.0% had moderate obstructive sleep apnea and only 8.0% had mild obstructive sleep apnea. Moreover, the number of desaturation (NOD) ranged from 0.0 to 783.0 with a mean of  $297.63 \pm 165.78$ , and the sleep time with O2 saturation <90% ranged from 0.0 to 100.0% with a mean of  $39.06 \pm 32.52$ , and the arousal index ranged from 16.0 to 736.0 events with a mean arousal index of  $180.01 \pm 118.83$ .

**Table 2** shows that, the age of the studied elderly patients ranged from 60 to 82 years. Females constituted 61.0% of the studied patients. And 82.0% were married. Illiteracy was prevailing among 55.0% and only 12.0% of them had high education. Also, 55.0% were residing in rural areas and 68.0% were not working at current. Moreover, there is statistically significant relation was found between mean anxiety and depression level and older adults' educational level, as illiterate had greater anxiety and depression level than others ( $p=0.004^*$  and  $p=0.001^*$  respectively). Also, there is statistical significant relation was found between mean anxiety level and geriatric patients' current work, as not working had greater anxiety level than

others ( $p=0.010^*$ ). On the other hand, there is no statistically significant relation was found between mean anxiety and depression level and older adults' age, social status, and residence.

**Table 3** shows that 65.0% of the studied elderly didn't use a denture, and 69.0% of them were taking caffeine. Also, 73.0% of the study's elderly were not smoking. And 96.0% were obese. Moreover, there is statistically significant relation was found between mean anxiety and depression level and older adults' using denture ( $p=0.001^*$  and  $p=0.003^*$  respectively). On the other hand, no statistically significant relation was found between mean anxiety and depression level and taking caffeine, smoking, and body mass index (BMI).

**Table 4** presents that there was a statistically positive significant correlation between daytime sleepiness, and anxiety level ( $p=0.001^*$ ) indicating that obstructive sleep apnea patients with excessive daytime sleepiness had a higher level of anxiety. Also, there was a statistically positive significant correlation between anxiety level and depression level ( $p<0.001^*$ ) indicating that obstructive sleep apnea patients with higher anxiety had a higher level of depression. Moreover, the table shows that there was a statistically positive significant correlation between anxiety and depression level and OSA severity ( $p<0.001^*$  and  $p<0.001^*$  respectively) indicating that patients with severe obstructive sleep apnea had a higher level of anxiety and depression.

**Table 5** shows the multivariate linear regression model for psychological health status. It was noticed from the table that OSA severity was a significant independent predictor for anxiety and depression ( $p<0.001^*$ ) and responsible

for 50% of anxiety and 40% of depression.

#### **Discussion**

Geriatric patients with obstructive sleep apnea can experience a deterioration of their mood, shown by symptoms of anxiety, and depression. The prevalence of depression varied from 7 to 63% and the prevalence of anxiety varied from 11 to 70% among patients<sup>10</sup>.

The present study showed that the majority of the studied elderly patients with OSA had anxiety. This result may be justified by OSA-related findings include bed partner symptoms, particularly loud snoring, breathing interruptions and frequent night awakens causing anxiety, and depression. This result is in accordance with a study done in Europa by Weaver et al., (2018)<sup>11</sup> who reported increased symptoms of anxiety in the sleep disorder group with obstructive sleep apnea up to 50%. Another study was done in Korea by Lee, Lee, Chung & Kim, (2015)<sup>12</sup> who found High rates of anxiety are present in the sample of OSA patients. Moreover, the present study showed that more than half of the studied patients had depression. This finding is in accordance with a study done in Germany by Acker et al., (2016)<sup>13</sup> who found high rates of depression present in OSA patients. Another study done in China by Cai, Xu, Wei, Sun & Chen, (2017)<sup>14</sup> found that Seventy-four elderly patients were diagnosed with obstructive sleep apnea had depression disorders. In contrast, a study was done in Spain by Rey de Castro & Rosales-Mayor, (2013)<sup>15</sup> reported that a high percentage of the patients included in the study had minimum or nonexistent depression and anxiety symptoms.

Concerning daytime sleepiness, the present study pointed that most of the studied patients had higher daytime sleepiness. This result may be justified as; EDS is a common complaint in patients with OSA. This result agrees with a study done in Turkey by Balcan & Ozsancak Ugurlu, (2017)<sup>16</sup> and In Italy by Angelelli et al., (2020)<sup>17</sup> who found that most of the studied elders were sleepy. In contrast, a study was done in France by Sforza, Pichot, Martin, Barthelemy & Roche, (2016)<sup>18</sup> reported that only 15% of the patients had excessive daytime sleepiness.

The majority of the studied patients in the present study had severe obstructive sleep apnea. This result may be justified as; the increase in Apnea Hypopnea Index with aging may be related to the increase in weight and the total number of respiratory arousals was significantly decreased in the elderly with OSA. The result of this study is in agreement with a study done in Japan by Hongyo et al, (2016)<sup>19</sup> and in Brazil by Zhao, Viana, Ma & Capasso, (2018)<sup>20</sup> who found that the severity of OSA in elderly patients increased with aging.

The present study showed that OSA was encountered more among elderly women than men. This result may be related to loss of the protective effects of female reproductive hormones after menopause. This result agrees with study done in Italy by Silvestri et al., (2019)<sup>21</sup>. In contrast, a study was done in USA by Heinzer et al., (2015)<sup>22</sup> reported that the prevalence of OSA is higher in elderly men than women.

Regarding the age of the studied geriatric patients, it was observed that age is the most important risk factor for developing OSA. This result agrees with a study done in Italy by Sunwoo et al., (2018)<sup>23</sup>. Also, a study done in Egypt by

Abbas, Zayed & Awad, (2020)<sup>24</sup> reported that OSA is more common with increasing age.

Anxiety and depression of geriatric patients with OSA may depend on several factors in terms of demographic characteristics. The present study pointed that; illiterate elderly patients had more anxiety and depression symptoms. This result is supported by a study was done in Spain by Lee, Han & Ryu, (2015)<sup>25</sup>. Another study done in Korea by Freeman et al., (2016)<sup>26</sup> reported that lower education was associated with an increased risk of depression at follow-up. Also, the current study demonstrated that anxiety and depression were more prevalent in females than in males but there is no statistically significant relation was found between anxiety and depression score and older adults' sex. This result is the same of a study done in Australia by Edwards et al., (2015)<sup>27</sup>.

Depression and anxiety were more prevalent in obese older adults with OSA but there is no statistically significant relation was found between depression and anxiety scores with older adults' BMI in the current study. This result is in agreement with a study done in Iran by Razaetalab et al., (2014)<sup>28</sup>. In contrast, in a study done in Pennsylvania by Björnsdóttir et al., (2016)<sup>29</sup>, found that there is a statistically significant relation was found between anxiety and depression scores and older adults' BMI.

The present study showed a statistically positive significant correlation between daytime sleepiness and anxiety level. The same result were reported in a study Korea by Lee, Han & Ryu, (2015)<sup>25</sup>, and a study done in turkey by Yazici & Hatipoglu, (2019)<sup>30</sup>. Moreover, the present study findings showed that there was a statistically

positive significant correlation between daytime sleepiness and obstructive sleep apnea severity. This result is supported by a study done in Poland by Gabryelska & Białasiewicz, (2020)<sup>31</sup>.

A statistically positive significant correlation between anxiety and depression scores and AHI was found in the current study. This result is supported by a study done in Greece by Diamanti et al., (2013)<sup>32</sup>. Also, another study was done in China by Dai et al., (2016)<sup>33</sup> found that there was a statistically positive significant correlation between depression scores and AHI.

In the multivariate linear regression model, the current study approved that obstructive sleep apnea severity (AHI) was a significant independent predictor for anxiety and depression. This result is supported by a study done in Australia by Edwards et al., (2015)<sup>28</sup> and another study was done in Netherlands by Luik., et al (2015)<sup>34</sup>.

#### V. Conclusion

Based on the results of the present study, it can be concluded that psychological symptoms include anxiety and depression are common among geriatric patients with obstructive sleep apnea. Also, a statistically significant correlation was found between psychological health status and daytime sleepiness as well as OSA severity. Moreover, Obstructive sleep apnea severity was proved to be a significant independent predictor for anxiety and depression.

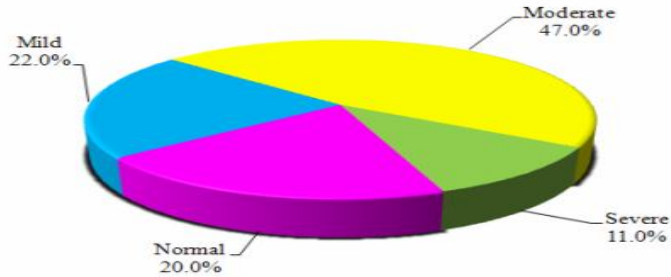
#### IV. Recommendations

- 1- Designing an educational program for obstructive sleep apnea geriatric patients about treatment adherence to improve their psychological health status.
- 2- Implementation of an intervention program for nursing staff about

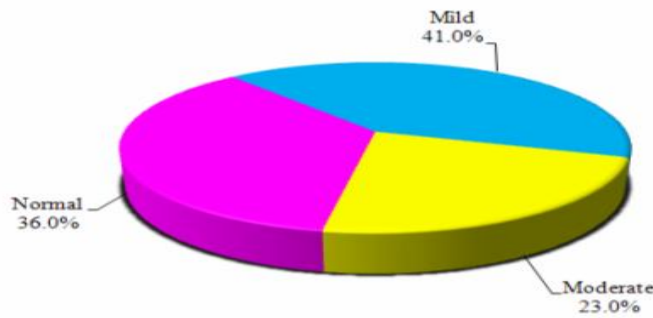
problems faced in caring for patients with obstructive sleep apnea to help them to provide optimal care and early screening of psychological problems.

**Acknowledgment**

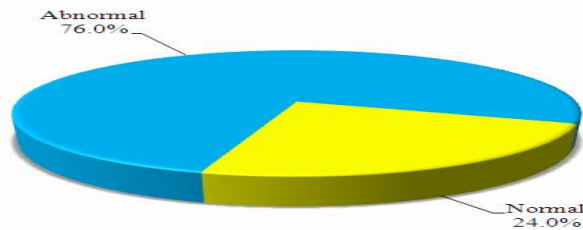
We would like to thank all health personnel in the outpatient clinic of the Chest Medicine Department at Main Mansoura University Hospital, Egypt as well as geriatric patients for their participation to fulfill this study.



**Figure 1:** Distribution of the studied geriatric patients with obstructive sleep apnea according to anxiety.



**Figure 2:** Distribution of the studied geriatric patients with obstructive sleep apnea according to depression.



**Figure 3:** Distribution of the studied geriatric patients with obstructive sleep apnea according to daytime sleepiness.



**Table1:Distribution** of the studied geriatric patients with obstructive sleep apnea according to their Polysomnography data (n=100)

Patient's Polysomnography Data	Min. – Max.	Mean ± SD.
<b>Sleep stages</b>		
Rapid eye movement (REM) (%)	0.0 – 74.50	9.71 ± 13.83
Light sleep (%)	25.50 – 100.0	86.42 ± 12.53
Deep sleep (%)	0.0 – 28.70	5.11 ± 7.30
<b>Sleep measures</b>		
Total sleep time (hours)	2.0 – 6.0	4.87 ± 1.08
<b>Apnea hypopnea index (AHI)</b>		
	<b>No.</b>	<b>%</b>
Mild (AHI ≥5≤15)	8	8.0
Moderate (AHI >15≤ 30)	14	14.0
Sever (AHI>30)	78	78.0
<b>Apnea hypopnea index (AHI)</b>	5.0 – 179.80	56.54 ± 29.93
<b>O2 saturation</b>		
Number of desaturation (NOD)	0.0 – 783.0	297.63 ± 165.78
Sleep time with O2 saturation <90%	0.0 – 100.0	39.06 ± 32.52
<b>Arousal index</b>	16.0 – 736.0	180.01 ± 118.83

**Table 2:** Relationship between demographic characteristics, and psychological health status of the studied geriatric patients with obstructive sleep apnea

Items	N= 100	Psychological Health Status	
		Anxiety Mean ± SD	Depression Mean ± SD
<b>Age</b>		11.53 ± 3.60	
60–	57	12.10 ± 4.43	8.88 ± 2.78
65–	21	12.88 ± 3.72	9.05 ± 2.87
70	17	14.60 ± 0.55	9.71 ± 3.24
More than 75	5		11.00 ± 2.00
<b>F(p)</b>		1.430(0.239)	1.099(0.353)
<b>Sex</b>		12.41 ± 3.91	9.31 ± 2.79
Female	61	11.44 ± 3.48	8.92 ± 2.98
Male	39		
<b>t(p)</b>		0.521(0.596)	0.696(0.501)
<b>social status</b>		11.94 ± 3.73	9.13 ± 2.91
Married	82	13.00 ± 4.24	9.83 ± 2.92
Widow	12	11.33 ± 3.44	8.17 ± 1.72
Divorced	6		
<b>F(p)</b>		0.521(0.596)	0.696(0.501)
<b>Educational level</b>		13.05 ± 3.26	9.95 ± 2.56
Illiterate	55	11.18 ± 4.16	8.70 ± 2.95
Read and write	33	9.67 ± 3.34	6.83 ± 2.52
High education	12		
<b>F(p)</b>		5.751*(0.004*)	7.327*(0.001*)
<b>Residence</b>		12.55 ± 3.77	9.16 ± 2.54
Rural	55	11.40 ± 3.70	9.16 ± 3.23
Urban	45		
<b>t(p)</b>		1.525(0.130)	0.014(0.989)
<b>Current work</b>		12.69 ± 3.73	9.49 ± 2.79
No	68	10.63 ± 3.49	8.47 ± 2.91
Yes	32		
<b>t(p)</b>		2.638*(0.010*)	1.676(0.097)

**Table 3:** Relationship between health-related history, and psychological health of the studied geriatric patients with obstructive sleep apnea

Items	N= 100	Psychological Health Status	
		Anxiety Mean ± SD	Depression Mean ± SD
<b>Using a denture</b>			
No	65	11.15 ± 3.76	8.55 ± 2.73
Yes	35	13.66 ± 3.23	10.29 ± 2.77
t(p)		3.489*(0.001*)	3.008*(0.003*)
<b>Taking caffeine</b>			
Yes	69	22.30 ± 4.17	11.84 ± 3.80
No	31	22.29 ± 2.81	12.45 ± 3.70
t(p)		0.750(0.455)	0.255(0.799)
<b>Smoking</b>			
No	73	12.37 ± 3.78	9.37 ± 2.79
Yes	27	11.11 ± 3.61	8.59 ± 3.02
t(p)		1.495(0.138)	1.211(0.229)
<b>BMI (Kg/m)</b>			
Obese(≥30)	96	12.13 ± 3.73	9.19 ± 2.84
Over weight (25-29.99)	3	11.00 ± 4.58	9.00 ± 4.36
Normal weight(18.5- 24.99)	1	6.0	7.0
F(p)		1.441(0.242)	0.291(0.748)

T: Student t-test                      F: F for ANOVA test  
 P: p-value for the association between different categories  
 \*: Statistically significant at  $p \leq 0.05$

**Table 4:** Correlation between day time sleepiness, psychological health status, and OSA severity

Items		Psychological health status		OSA severity
		Anxiety	Depression	
Day time sleepiness	R	0.332*	0.175	0.256*
	P	0.001*	0.082	0.010*
Anxiety	R		0.800*	0.695*
	P		<0.001*	<0.001*
Depression	R			0.632*
	P			<0.001*

R: Pearson coefficient  
 \*: Statistically significant at  $p \leq 0.05$   
 OSA: obstructive sleep apnea

**Table 5:** Multivariate Linear regression model for the psychological health status

Anxiety	B	Beta	T	P
Day time sleepiness	0.106	0.165	2.238*	0.028*
Obstructive sleep apnea severity (AHI)	0.082	0.009	8.860*	<0.001*
R2 = 0.511 , F =50.710* , p <0.001				
Depression	B	Beta	T	P
Day time sleepiness	0.007	0.014	0.169	0.866
Obstructive sleep apnea severity (AHI)	0.060	0.629	7.726*	<0.001*
Day time sleepiness	0.007	0.014	0.169	0.866
R2 = 0.508 , F =50.131* , p <0.001*				

F, p, and p values for the model                      R2: Coefficient of determination

Beta: Standardized Coefficients

B: Unstandardized Coefficients

t: t-test of significance

\*: Statistically significant at  $p \leq 0.05$

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