

OBSTRUCTIVE SLEEP APNEA AWARENESS AND KNOWLEDGE AMONG A SAMPLE GENERAL POPULATION IN SAUDI ARABIA

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Abstract

Background: Obstructive Sleep Apnea (OSA) is a partial or complete blockage of the upper airway while sleeping. The upper airways collapse while sleeping because of a reduction in airway muscle tone, particularly in the inspiratory breathing stage. This study aims to investigate the general population's awareness and knowledge about OSA in a sample of general population in Saudi Arabia. **Methods:** The present questionnaire-based study was accomplished at the Faculty of Medicine Rabigh, KAU, Jeddah, KSA. A validated questionnaire, OSAKA, was used. The online questionnaire (Google form) was distributed via social media platforms. The questionnaire comprised of 33 questions. **Results:** The mean age of study participants was 34.98 ± 11.39 years, including 492 (49.9%) females and 493 (50.1%) males). Among the participants, 81 (8.2%) were underweight, 388 (39.4%) were normal weight, 331 (33.6%) were overweight, and 185 (18.8%) were obese. Only 62 (6.3%) participants were diagnosed with OSA. Other characteristics of the participants are given in Table 1. About one-third of the participants, 306 (31.1%), did not know the estimated prevalence of OSA. One-quarter of the participants, 256 (26%), were not aware of the gold standard for diagnosing OSA. Regarding participants' knowledge of OSA symptoms, the participants' responses were apnea (646, 65.6%), snoring (556, 56.4%), daytime fatigue (429, 43.6%), a feeling of suffocation during sleep (696, 70.7%), and others. More than 90% of the participants showed positive attitudes in questions related to attitude. **Conclusion:** The study found a 6.3% prevalence of OSA among study participants. The participants demonstrated satisfactory knowledge about the common symptoms of OSA; however, insufficient understanding of its complications was apparent among the majority of the participants. Overweight participants showed significantly higher knowledge about the complications associated with OSA. There was a positive attitude towards knowledge and awareness about OSA. There is a need for increased public awareness about obstructive sleep apnea and its complications for early treatment and management, hence, better health outcomes and quality of life.

Keyword: OSP, BMI, Attitudes, Awareness, OSAKA

Introduction:

Obstructive Sleep Apnea (OSA) is a partial or complete blockage of the upper airway while sleeping. The upper airways collapse while sleeping because of a reduction in airway muscle tone, particularly in the inspiratory breathing stage (Nufaiei, 2023). In addition to loud snoring accompanying strangling or breath gasping for air, OSA causes repeated fragmented sleep and recurrent awakenings. Interrupted sleep may lead to tiredness, headaches, and even cognitive impairment (Sawan et al., 2023). It has been identified as an indicator of risk for many medical conditions, including hypertension, stroke, heart disease, diabetes mellitus, car crashes, daytime hypersomnia, and worsening of a person's quality of life (Marran et al., 2019). Despite its widespread prevalence, OSA is a risky disease that is usually neglected. OSA's higher prevalence is gradually emerging as an international health epidemic, mainly because of the current worldwide epidemic of obesity (Al-Rasheedi et al., 2022).

Its prevalence differs depending on geographical locations and demographic variables. Still, approximately 425 million individuals aged 30 to 69 have moderate to severe OSA (2), and among the entire adult population, 80% to 90% of OSA remains untreated and undiagnosed (Pivetta et al., 2021). The average number of OSA symptoms in Saudi Arabia's adult population is 26.9%, with the average age of participants being 30 years. Mild, moderate, and severe excessive sleepiness during the day appeared in 12.5%, 8.3%, and 6.1%, based on the severity of OSA symptoms (Nufaiei, 2023). The prevalence of OSA in Saudi Arabia has been estimated as 8.8% (12.8% in men and 5.1% in women) (Alhejaili et al., 2021). In a study, most participants believed that OSA is a sign of fatigue. The study showed insufficient knowledge of OSA (Alshehri et al., 2023). Another Saudi study from the Jizan Region reported that 60% were had inadequate knowledge of OSA. The researchers found that most people had no reliable sources of knowledge, and medical professionals should try harder to raise public awareness regarding OSA. Additionally, a study with a wider population is required to evaluate OSA awareness levels (Azyabi et al., 2023).

A Chinese study reported that 89.4% of the respondents desired to gain knowledge about OSA, and the majority expressed concern regarding its cause (Pan et al., 2023). A South African study reported that primary care physicians had a limited understanding of both adult and pediatric OSA; they believed that OSA was significant and had little faith in the adult and pediatric management of the condition (Chang et al., 2020).

Literature indicates people's knowledge is not up to the mark about OSA. We designed the present study to improve Saudi residents' knowledge and attitude. This study aims to investigate the general population's awareness and knowledge about OSA in Saudi Arabia. The findings will provide important insights into the frequency and awareness of OSA in Saudi Arabia's general population.

Methodology:

The present questionnaire-based study was accomplished at the Faculty of Medicine Rabigh, KAU, Jeddah, KSA. The ethical approval was taken from the bioethics and research committee of KAU, Jeddah.

The sample size was calculated with a 95% confidence level and 5% margin of error using the formula: $n = P(1-P) * Z_{\alpha}^2 / d^2$. The estimated sample size was 384. The inclusion criteria were individuals of 18 or >18 years old and residing in KSA. The incomplete questionnaires were excluded from the study.

The OSAKA questionnaire was used which already an validated questionnaire. from the already published study (REF). The question was translated from English to Arabic and back translated with the help of two bilingual experts to minimize the chance of misunderstanding the translation. A pilot

study was conducted on 50 subjects to explore the questionnaire's comprehensibility.

The online questionnaire (Google form) was distributed via social media platforms. The brief objective of the study was mentioned at the start of the questionnaire, and a consent statement was also given. It was mentioned to the respondents that completing the study's questionnaire would be considered their consent to participate in the study voluntarily. The questionnaire comprised of 33 questions. 9 Qs related to symptoms knowledge, and its point distribution was like "Yes=1 point, no=0 point, I don't know=0 point" and total points 9 (60% 5 points or more were considered satisfactory and less than 5 points were considered unsatisfactory knowledge about symptoms). 6 Qs related to complications knowledge and its point distribution was like "Yes=1 point, no=0 point, I don't know=0 point" and total points 6 (60% 4 points or more were considered satisfactory and less than 4 points considered unsatisfactory knowledge about complications). 15 Qs related to general knowledge and its point distribution was like "Yes=1 point, no=0 point" and total points 15 (60% 9 points or more were considered satisfactory and less than 9 points considered unsatisfactory knowledge). 3 Qs related to attitude and its point distribution was like "Agree=1 point, disagree=0 point" and total points 3 (60%, 2 points or more were considered positive attitude and less than 2 points considered negative attitude).

Statistical analysis:

The data were analyzed using Statistical Package for the Social Sciences 24 (SPSS Inc., Chicago, IL, USA). The qualitative data were expressed as frequencies and percentages, while quantitative data were expressed as means and standard deviations. Gender-wise and BMI-wise comparisons of participants' satisfactory and unsatisfactory scores regarding OSA Knowledge (symptoms, complications, general) and attitude were compared with the Chi-square test. The association of variables with participants' satisfactory knowledge scores was measured by binary logistic regression analysis. The level of significance was taken <0.05 .

Results:

The mean age of study participants was 34.98 ± 11.39 years, and there was almost an equal gender participation (492, 49.9% females and 493, 50.1% males). Among the participants, 81 (8.2%) were underweight, 388 (39.4%) were normal weight, 331 (33.6%) were overweight, and 185 (18.8%) were obese. Only 62 (6.3%) participants were diagnosed with OSA. Other characteristics of the participants are given in Table 1.

Table 1: General characteristics of the participants (n=985)

Variables		Mean \pm SD	Range
Age (years)		34.98 \pm 11.39	18-80
		Frequency	Percentage
Gender	Female	492	49.9
	Male	493	50.1
Nationality	Non-Saudi	30	3.0
	Saudi	955	97.0
Region	Central Region	24	2.4

	Eastern Province	91	9.2
	Southern area	400	40.6
	The northern area	30	3.0
	Western Region	440	44.7
BMI	Underweight	81	8.2
	Healthy weight	388	39.4
	Over weight	331	33.6
	Obese	185	18.8
What is your educational status?	No formal education	4	0.4
	High school and below	180	18.3
	Master's	78	7.9
	Ph.D.	16	1.6
	Student	31	3.1
	University	676	68.6
What is your profession?	Business man/woman	19	1.9
	Government employee	465	47.2
	Health care worker	12	1.2
	housewife	53	5.4
	Not employed	69	7.0
	private job	130	13.2
	Student	237	24.1
Marital status	A widower	10	1.0
	Divorced	29	2.9
	Married	589	59.8
	Single	357	36.2
Have you ever been diagnosed with obstructive sleep apnea?	no	923	93.7
	Yes	62	6.3

About one-third of the participants, 306 (31.1%), did not know the estimated prevalence of OSA. One-quarter of the participants, 256 (26%), were not aware of the gold standard for diagnosing OSA. A significant number of participants did not know the different treatment options for OSA. More than 60% (604) believed that untreated obstructive sleep apnea is correlated with a higher rate of car-related accidents. More than half of the participants (558, 56.6%) believed that a neck size greater than 17 inches is associated with OSA in males. Almost half of the participants (485, 49.2%) stated that females suffer from OSA more than males. Regarding participants' knowledge of OSA symptoms, the participants' responses were apnea (646, 65.6%), snoring (556, 56.4%), daytime fatigue (429, 43.6%), a feeling of suffocation during sleep (696, 70.7%), uncomfortable or interrupted sleep (527, 53.5%), daytime sleepiness (273, 27.7%), disturbed concentration (354, 35.9%), morning headaches (362, 36.8%), and obesity (592, 60.1%). Regarding participants' knowledge of OSA complications, the participants' responses were stroke (501, 50.9%), diabetes (239, 24.3%), high blood pressure (356, 36.1%), dementia (253, 25.7%), irregular heartbeat (481, 48.8%), and myocardial infarction (433, 44%) (Table 2).

Table 2: Participants knowledge regarding OSA (general, symptoms, complications) (n=985)

Statements	No/Yes	Frequency	Percentage
Participants general knowledge regarding OSA			
K1 The estimated prevalence of obstructive sleep apnea in adults ranges between 2% and 10%?	No	306	31.1
	Yes	679	68.9
K2 The gold standard for diagnosing obstructive sleep apnea is an overnight sleep study?	No	256	26.0
	Yes	729	74.0
K3 Is continuous positive airway pressure (CPAP) the first-line treatment for severe obstructive sleep apnea?	No	313	31.8
	Yes	672	68.2
K4 Is laser-assisted uvuloplasty an appropriate treatment for severe obstructive sleep apnea?	No	389	39.5
	Yes	596	60.5
K5 Could sleep apnea be caused by a loss of upper airway muscle tone during sleep?	No	243	24.7
	Yes	742	75.3
K6 In children, do adenoids and large tonsils often cause obstructive sleep apnea?	No	215	21.8
	Yes	770	78.2
K7 A useful examination in suspected obstructive sleep apnea is a cranial and oropharyngeal examination?	No	253	25.7
	Yes	732	74.3
K8 Does alcohol at bedtime improve obstructive sleep apnea?	No	651	66.1
	Yes	334	33.9
K9 Does continuous positive airway pressure (CPAP) treatment cause nasal congestion?	No	410	41.6
	Yes	575	58.4
K10 Is there a correlation between untreated obstructive sleep apnea and a higher rate of car-related accidents?	No	381	38.7
	Yes	604	61.3
K11 Is a neck size greater than 17 inches associated with obstructive sleep apnea in males?	No	427	43.4
	Yes	558	56.6
K12 Do females suffer from obstructive sleep apnea more than males?	No	500	50.8
	Yes	485	49.2
K13 Is it normal for adults to have five interruptions or shortness of breath during sleep in one hour?	No	507	51.5
	Yes	478	48.5
K14 Is there a link between untreated obstructive sleep apnea and arrhythmia?	No	297	30.2
	Yes	688	69.8
K15 Uvulopalatopharyngoplasty is a treatment for most patients suffering from obstructive sleep apnea?	No	290	29.4
	Yes	695	70.6
Participants knowledge regarding OSA symptoms			
Q1S Apnea is one of the symptoms of OSA	No	339	34.4
	Yes	646	65.6
Q2S Snoring is a symptom of OSA	No	429	43.6
	Yes	556	56.4
Q3S Daytime fatigue is a symptom of OSA	No	556	56.4
	Yes	429	43.6
Q4S The feeling of suffocation during sleep is one of the symptoms of obstructive sleep apnea (OSA).	No	289	29.3
	Yes	696	70.7

Q5S Uncomfortable or interrupted sleep is a symptom of obstructive sleep apnea (OSA).	No	458	46.5
	Yes	527	53.5
Q6S Daytime sleepiness is a symptom of obstructive sleep apnea (OSA).	No	712	72.3
	Yes	273	27.7
Q7S Disturbed concentration is a symptom of obstructive sleep apnea (OSA).	No	631	64.1
	Yes	354	35.9
Q8S Morning headaches are a symptom of obstructive sleep apnea (OSA).	No	623	63.2
	Yes	362	36.8
Q9S Obesity is a symptom of obstructive sleep apnea (OSA).	No	393	39.9
	Yes	592	60.1
Participants knowledge regarding OSA complications			
Q1C Stroke is one of the complications of OSA	No	484	49.1
	Yes	501	50.9
Q2C Diabetes is a complication of OSA	No	746	75.7
	Yes	239	24.3
Q3C High blood pressure is a complication of obstructive sleep apnea (OSA).	No	629	63.9
	Yes	356	36.1
Q4C Dementia is a complication of obstructive sleep apnea (OSA).	No	732	74.3
	Yes	253	25.7
Q5C An irregular heartbeat is a complication of obstructive sleep apnea (OSA).	No	504	51.2
	Yes	481	48.8
Q6C Myocardial infarction is a complication of obstructive sleep apnea (OSA).	No	552	56.0
	Yes	433	44.0

More than 90% of the participants showed positive attitudes in questions related to attitude. They agreed that it is an important disease and necessary to diagnose it and agreed to OSA screening (Table 3).

Table 3: Participants attitude regarding OSA (n=985)

Statements	Agree/ disagree	Frequency	Percentage
A1 Obstructive sleep apnea (OSA) is considered an important disease?	Disagree	70	7.1
	Agree	915	92.9
A2 Is it necessary to diagnose people with obstructive sleep apnea OSA?	Disagree	79	8.0
	Agree	906	92.0
A3 If a health facility is available, would you prefer to be screened for OSA?	Disagree	86	8.7
	Agree	899	91.3

There was no significant difference in gender-wise comparison of participants' OSA knowledge (symptoms, complications, general) and attitude (Table 4).

Table 4: Gender wise comparison of participants' scores regarding OSA Knowledge (symptoms, complications, general) and attitude (n=985)

Variables	Satisfactory/ Unsatisfactory	Gender			P-value
		Females (n=492)	Males (n=493)	Total (n=985)	
Symptoms Knowledge Score	Satisfactory	243(49.4%)	233(47.3%)	476(48.3%)	0.504
	Unsatisfactory	249(50.6%)	260(52.7%)	509(51.7%)	
Complications Knowledge Score	Satisfactory	136(27.6%)	144(29.2%)	280(28.4%)	0.586
	Unsatisfactory	356(72.4%)	349(70.8%)	705(71.6%)	
General Knowledge Score	Satisfactory	308(62.6%)	326(66.1%)	634(64.4%)	0.248
	Unsatisfactory	184(37.4%)	167(33.9%)	351(35.6%)	
Attitude Score	Positive	462(93.9%)	467(94.7%)	929(94.3%)	0.577
	Negative	30(6.1%)	26(5.3%)	56(5.7%)	

BMI-wise comparison of participants' OSA knowledge (symptoms, complications, general) and attitude showed a significant difference in complication-related knowledge according to BMI categories ($p=0.014$). The participants from all BMI categories had significantly positive attitudes ($p=.026$) (Table 5).

Table 5: BMI wise comparison of participants' scores regarding OSA Knowledge (symptoms, complications, general) and attitude (n=985)

Variables	Satisfactory/ Unsatisfactory	BMI categories					P-value
		Underweight (n=81)	Healthy weight (n=388)	Over weight (n=331)	Obesity (n=185)	Total (n=985)	
Symptoms Knowledge Score	Satisfactory	41	196	154	85	476	0.623
		50.6%	50.5%	46.5%	45.9%	48.3%	
	Unsatisfactory	40	192	177	100	509	
		49.4%	49.5%	53.5%	54.1%	51.7%	
Complications Knowledge Score	Satisfactory	23	91	114	52	280	0.014
		28.4%	23.5%	34.4%	28.1%	28.4%	
	Unsatisfactory	58	297	217	133	705	
		71.6%	76.5%	65.6%	71.9%	71.6%	
General Knowledge Score	Satisfactory	53	244	215	122	634	0.882
		65.4%	62.9%	65.0%	65.9%	64.4%	
	Unsatisfactory	28	144	116	63	351	
		34.6%	37.1%	35.0%	34.1%	35.6%	
Attitude Score	Positive	72	361	320	176	929	0.026
		88.9%	93.0%	96.7%	95.1%	94.3%	
	Negative	9	27	11	9	56	

		11.1%	7.0%	3.3%	4.9%	5.7%	
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There was a significant positive relationship between general knowledge scores and attitude scores ($p < 0.001$). The participants who had satisfactory knowledge had positive attitudes.

Table 6: Relationship between Knowledge Scores and attitudes

General Knowledge Score	Attitude Score		Total	P-value
	Positive	Negative		
Satisfactory	620	14	634	<0.001
	62.9%	1.4%	64.4%	
Unsatisfactory	309	42	351	
	31.4%	4.3%	35.6%	
Total	929	56	985	
	94.3%	5.7%	100.0%	

The binary logistic regression analysis assessed the association of various variables with participants' satisfactory knowledge scores. Compared to the Western region, living in the Eastern region suggests significantly lower odds of satisfactory knowledge ($\beta = -1.245$, OR = 0.288, $p < 0.001$). Other variables such as gender, education level, BMI, profession, and marital status do not show a statistically significant association with knowledge scores.

Table 7: Association of variables with participants' satisfactory knowledge scores (binary logistic regression).

Variables	Categories	Beta coefficient(B)	Odds Ratio	P-value	95% C.I.for EXP(B)	
					Lower	Upper
Gender	Male	0.154	1.166	0.248	0.898	1.514
	Female		1			
Education	High school and below	-0.198	0.820	0.269	0.578	1.166
	Master's	0.047	1.048	0.850	0.645	1.702
	Ph.D.	-0.527	0.590	0.366	0.188	1.850
	Student	0.377	1.458	0.308	0.706	3.009
	University		1			
Region	Central Region	0.128	1.137	0.767	0.486	2.658
	Eastern Province	-1.245	0.288	0.000	0.152	0.545
	Southern area	0.275	1.317	0.054	0.995	1.742
	The northern area	0.506	1.658	0.183	0.788	3.488
	Western Region		1			
BMI	Underweight	0.023	1.023	0.935	0.590	1.773
	Healthy weight	0.134	1.143	0.476	0.792	1.650
	Overweight	0.044	1.045	0.821	0.715	1.526
	Obesity		1			

Profession	Business man/woman	-0.228	0.796	0.655	0.292	2.169
	Government employee	-0.063	0.939	0.707	0.678	1.301
	Health care worker	0.545	1.724	0.358	0.539	5.511
	housewife	0.202	1.224	0.515	0.667	2.245
	Not employed	-0.214	0.807	0.462	0.456	1.429
	private job	-0.125	0.882	0.584	0.563	1.382
	Student		1			
Marital Status	A widower	0.176	1.193	0.788	0.330	4.305
	Divorced	-0.060	0.942	0.882	0.425	2.087
	Married	-0.016	0.984	0.908	0.748	1.295
	Single		1			

The knowledge scores are treated as a dichotomous variable (satisfactory vs. unsatisfactory).

Discussion:

Obstructive Sleep Apnea (OSA) is a sleep disorder marked by irregular breathing patterns and insufficient oxygen delivery to the body. If left untreated, this condition can result in serious health problems, given that the blockage of airways during sleep prevents sufficient oxygen supply in the body (Sharma et al., 2015). This study aims to assess Saudi Arabia's general population's knowledge and awareness of OSA. It is essential to comprehend the population's level of awareness of the condition in order to identify any gaps in its management and develop evidence-based strategies and policies that address the challenges associated with the disorder; this will go a long way in creating effective interventions that deliver sustainable health outcomes in the population (Patil et al., 2019).

In the current study, the prevalence rate of obstructive sleep apnea was reported to be 62 (6.3%), which is almost within the projected 9–10% global prevalence and is considered to be a serious public health concern (Sohail et al., 2020). The results of the study were consistent with those of a survey by (Desalu et al., 2016), which found that participants had a higher-than-average level of awareness regarding both the diagnosis and estimated prevalence of OSA.

In our study, a substantial proportion of participants demonstrated general knowledge about obstructive sleep apnea (OSA). However, a significant minority lacked sufficient understanding of its symptoms, diagnosis, treatment options, and associated risks and complications. The findings revealed that nearly three-quarters of participants 729 (74.0%) recognized that an overnight sleep study is the gold standard for diagnosing OSA, while nearly one-quarter 256 (26%) were unaware of this diagnostic method. These results align with a study conducted in Saudi Arabia by Al-Rasheedi et al., which found that more than three-fourths (78%) of participants also recognized the overnight sleep study as the gold standard for diagnosing OSA.

Regarding familiarity with various treatment options, a considerable proportion of participants demonstrated insufficient knowledge, particularly about first-line treatments and appropriate options for severe OSA. Similar observations were noted in a study conducted in China by Sia et al., which reported that while about 21.5% of respondents were aware of OSA, only 110 (8.4%) could correctly identify a treatment option (Sia et al., 2017). This underscores the need for targeted educational efforts concerning the diagnosis and treatment of OSA.

The study found that a notable proportion of participants 604 (60%) believed that untreated obstructive sleep apnea is correlated with a higher rate of car-related accidents. Additionally, more than half of the participants 558 (56.6%) believed that a neck size greater than 17 inches is associated with OSA in

males. Furthermore, nearly half of the participants 485 (49.2%) noted that females suffer from OSA more than males, which is consistent with findings by McKinney et al., who reported a higher prevalence of OSA in females than in males (62% in females vs. 24% in males) (McKinney et al., 2015). The common symptoms reported in the current study included a feeling of suffocation during sleep 696 (70.7%); apnea 646 (65.6%); and uncomfortable or interrupted sleep 527 (53.5%), which agrees with Wali et al., who identified snoring, discomfort during sleep, and poor-quality sleep as the main signs of obstructive sleep apnea (Wali et al., 2017).

Regarding the complications, stroke was correctly reported by nearly half 501 (50.9%) of the participants; however, the majority of the participants were not aware of other complications caused by OSA. This underscores the need for enhanced public health education and awareness campaigns on Obstructive Sleep Apnea and its associated complications (Shehata et al., 2019). The study noted a positive attitude towards gaining knowledge about OSA, as more than 90% of the participants agreed to the need for diagnosis and also expressed their willingness and desire to be screened for OSA.

The study found significant differences in knowledge of OSA complications across the BMI categories ($p=0.014$). Of participants who were overweight, 114 (34.4%) demonstrated significantly more satisfactory knowledge about OSA complications than other groups. This suggests that overweight participants are more likely to understand the complications associated with OSA than other groups because they have a higher risk of developing and experiencing the condition (Knowledge of Signs, Symptoms, Risk Factors, and Complications of Obstructive Sleep Apnea among Dental Interns - PubMed, n.d.). Participants showed a significantly positive attitude across all BMI groups ($p=.026$). The binary logistic regression analysis assessed the association of various variables with participants' satisfactory knowledge scores. Compared to the Western region, living in the Eastern region suggests significantly lower odds of satisfactory knowledge ($\beta = -1.245$, $OR = 0.288$, $p < 0.001$).

The study's primary constraints and limitation stemmed from its adoption of a cross-sectional study design, which is limited in its ability to discern causal links between components. Due to the online surveys used in this study it was dependent on participants accurately recording their responses without the possibility of double-checking, which could have led to bias.

Conclusion:

The study found a considerably above-average prevalence of OSA awareness among the general population in Saudi Arabia. The participants demonstrated satisfactory knowledge about the common symptoms of OSA; however, insufficient understanding of its complications was apparent among the majority of the participants. BMI was found to be a risk factor for OSA. Overweight participants showed significantly higher knowledge about the complications associated with OSA. There was a positive attitude towards knowledge and awareness about OSA, with the significant majority expressing willingness to be screened for the condition. There is a need for increased public awareness about obstructive sleep apnea and its complications for early treatment and management, hence, better health outcomes and quality of life.

Acknowledgement:

We acknowledge all of the volunteers who provided samples for this research.

Funding:

This study was not supported by any outside sources.

Conflict of interests:

The authors declare no conflict of interest.

Informed consent:

Written informed consent was acquired from each individual study participant.

Data and materials availability:

All data associated with this study are present in the paper.

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