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Research Article

The Risk for Obstructive Sleep Apnea and Cognitive Function of High School Student

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ABSTRACT

Obstructive sleep apnea (OSA) is a common sleep disorder characterized by recurrent partial and/or total upper airway obstruction during sleep resulting in hypoxemia and arousal. One of the risk factors for OSA is obesity which its prevalence increased in Indonesia. OSA has a negative effect on cognitive function broadly. This study was aimed to determine the association between risk for OSA and cognitive function in high school students with obesity at Sulthon Aulia Boarding School, Bekasi. The study used a cross-sectional design and a simple random sampling technique. Data were taken using the Berlin Questionnaire and the Montreal Cognitive Assessment Indonesia version (MoCA-Ina) Questionnaire. The sample size is 47 subjects with inclusion criteria had overweight or obese body mass index (BMI) and were willing to be the research subjects. Subjects with a history of head injury, smoking, drinking alcohol, and taking sedative drugs were excluded from the study. There were differences in BMI and neck circumference between high-risk subjects for OSA and low-risk subjects for OSA. The risk level for OSA was significantly associated with cognitive function (p = 0.001; OR =12.727). High-risk subjects for OSA are recommended to lose weight and perform a polysomnographic evaluation.

Keywords : cognitive function, student, obesity, obstructive sleep apnea

INTRODUCTION

Obstructive sleep apnea (OSA) is a disorder characterized by repeated partial or total upper airway collapse that occurs during sleep. This causes loud snoring or choking that OSA patients often wake up from sleep and experience excessive daytime sleepiness. When obstruction of the airway occurs, the inspiratory airflow can be either reduced (hypopnea) or completely absent (apnea) (Mannarino *et al.,* 2012). OSA is a risk factor for cardiovascular disease, hypertension, coronary heart disease, congestive heart failure, and stroke. Excessive daytime sleepiness is a major

disorder affecting the quality of life, social function, and cognitive function of OSA patients (Duran-Cantolla *et al.,* 2017).

Several studies demonstrated a significant relationship between OSA and cognitive function (Ferini-Strambi *et al.,* 2003). Cognitive function is the ability to recognize or identify objects or circumstances or situations that are associated with learning experiences and one's intellectual capacity. Cognitive functions include memory, attention, orientation, language skills, numeracy, visuospatial, executive functions, abstraction, and intelligence (Wreksoatmojo, 2016). The decline of cognitive function in OSA patients can be measured using the Montreal Cognitive Assessment Indonesian version (MoCA-Ina) questionnaire. The MoCA-Ina questionnaire was very sensitive and specific in measuring mild cognitive impairment compared to the Mini-Mental State Examination (MMSE). Some cognitive domains, namely executive function, visuospatial, language, memory, attention, abstraction, and orientation can be assessed using MoCA-Ina. It takes approximately 10 minutes to perform 30 items of cognitive function tests with MoCA-Ina (Husein *et al.,* 2010; Hollis *et al.,* 2015).

Combining clinical assessment and objective observation of respiratory disorders that occur during sleep is needed to diagnose OSA. Polysomnographic monitoring is the gold standard for diagnosing OSA. According to the American Academy of Sleep Medicine, OSA is diagnosed if the patients have an apnea-hypopnea index (AHI) > 5 (Thropy *et al.,* 2001). However, polysomnography has limitations considering that it is expensive and time-consuming. The questionnaire is a simple and practical screening tool for detecting OSA. This study uses the Berlin questionnaire as an instrument to detect the risk level for OSA. It consists of several questions in three categories, namely symptoms of snoring, excessive daytime sleepiness, and a history of high blood pressure. The Berlin questionnaire had a sensitivity of 86%, a specificity of 77% and a positive predictive value of 89% (Netzer *et al.,* 1999).

The prevalence of OSA varies greatly in various countries. A literature review of eleven epidemiological studies published between 1993-2013 showed the prevalence of OSA with AHI > 5 is an average of 22% (range 9-37%) in men and 17% (range 4-50%) in women. OSA is more common in men than in women with a ratio of 2:1 (Karl *et al.,* 2015). Other systematic review studies showed that the prevalence of OSA ranges from 9-38%, is higher in men and obese subjects, and increases with age (Senaratna *et al.,* 2017). The result of the study was showed that the prevalence of undiagnosed OSA in the population was much greater because of a lack of awareness and limited access to sleep centers (Simpson *et al.,* 2013). At present, there is no prevalence of OSA data in Indonesia. A study was conducted using the Stop-Bang questionnaire in the population over the age of 35 in five areas of Jakarta showed that 49.5% of 202 subjects with a high-risk for OSA (Gunawan *et al.,* 2014). A similar study using the Berlin questionnaire on traffic police in East Jakarta showed that 17.2% of 93 subjects with a high-risk for OSA (Susanto *et al.,* 2016).

Obesity is a major risk factor for OSA and in general OSA patients are overweight (Karl *et al.,* 2015). Obese patients are subjected to have an increase in fat mass in the lateral wall of the pharynx that causes an increase in pharyngeal collapsibility resulting in pharyngeal narrowing (Patil *et al.,* 2007). Studies in Japan population showed that neck circumference is related to OSA severity regardless of the influence of obesity (Kawaguchi *et al.,* 2011). From 2007 to 2018, there is an increase in the proportion of overweight and obesity in population aged > 18 years in Indonesia. In 2018 the proportion of overweight was 13.6% and the proportion of obese was 21.8% in Indonesia (Kemenkes, 2018).

Based on these rationales, a study was conducted to determine the relationship between the risk level for OSA and cognitive function in students with obesity. This study was conducted at SMA Sulthon Aulia Boarding School, Bekasi. Considering that the students are living in a dormitory, their nutritional intake, daily activities, and stress level are relatively the same. Thus, the researchers can control some factors that affect cognitive function.

METHODS

This study uses a cross-sectional design in students with obesity at Sulthon Aulia Boarding School High School in 2019. Inclusion criteria were subjects with an overweight or obese body mass index (BMI) who are willing to be the research subject. Exclusion criteria were subjects with a history of head injury, smoking, drinking alcohol, and taking sedative drugs.

Sample size was determined by unpaired categorical analytic formulas with $\alpha = 5\%$, $\beta = 80\%$, P1 = 0.95 and P2 = 0.65. P1 and P2 values were taken from a previous study (Setyaningrum *et al.*, 2017). A number of 42 people were obtained according to the calculation. The results of the calculation are added by 10% to anticipate drop out so that the sample size is 47 people. This study has been approved by the Health Research Ethics Committee of Universitas Pembangunan Nasional 'Veteran' Jakarta (No.: B/1746/3/2019/KEPK) along with the permission from the Sulthon Aulia Boarding School High School principal. Data was collected directly from the research subjects using the MoCA-Ina questionnaire for cognitive function data and the Berlin questionnaire for OSA risk level data. Data were selected using a simple random sampling technique.

This study was conducted at Sulthon Aulia High School Boarding School on Jl. Batu Tumbuh I, Kecamatan Pondok Gede, Jaticempaka, Pondok Gede, Bekasi in March 2019. The analysis was carried out to describe the characteristics of the research subject and determine the relationship between the OSA risk level and cognitive function. Research variables are categorized based on previous research (Table 1).

Table 1. Operational Definition of Variables

No	Variable	Definition	Instrument	Method	Result	Scale
1.	OSA Risk Level	OSA risk level is classified based on findings from three symptom categories, namely: snoring, excessive daytime sleepiness, and a history of high blood pressure (Netzer *et al.,* 1999).	Berlin questionnaire	Subjects were asked to fill out a questionnaire assisted by roommates as the witness.	1. Low risk for OSA if the subject has none or only one positive category 2. High risk for OSA if the subject has two or more positive categories (Netzer *et al.,* 1999)	Nominal
2.	Cognitive Function	Cognitive function is the ability to recognize or identify objects or circumstances or situations that are associated with learning experiences and one's intellectual capacity (Wreksoat modjo, 2016)	MoCA-Ina questionnaire	Filling out the MoCA-Ina questionnaire by the subject guided by the researcher.	1. Disturbed (score < 26) 2. Normal (score > 26) (Husein *et al.*, 2010)	Nominal

RESULTS AND DISCUSSION

A total of 25 subjects were at low risk for OSA and 22 subjects were at high risk for OSA. There were differences in BMI and neck circumference between high-risk and low-risk subjects for OSA, but no differences in age and sex (Table 2).

Table 2. Research Subjects Characteristics Comparison

Variables	OSA Risk Level		P
	High (n = 22)	Low (n = 25)	
Age (median; min–max)	18 (15-18)	16 (16-19)	0.271
Sex, n (%)			
1. Male	10 (45.45)	11 (44)	0.920
2. Female	12 (54.54)	14 (56)	
BMI, n (%)			
1. Overweight	6 (27.27)	14 (56)	0.027
2. Obese 1	10 (45.45)	9 (36)	
3. Obese 2	6 (27.27)	2 (8)	
Neck Circumference (mean±SD)	35.7±3.9	33.5±2.8	0.029

This study showed that 46.8% (22 of 47 subjects with obesity) were at high risk for OSA (Table 2). This result is in line with a study conducted in obese subjects aged between 8-13 years in Toronto, Canada which also showed a high prevalence of OSA (53%) (Narang *et al.,* 2013). There was also a difference in BMI between high-risk subjects for OSA and low-risk subjects for OSA in this study. Subjects with high-risk for OSA were more obese compared to subjects with low risk for OSA (Table 2). These results are consistent with the results of research that obesity is a major risk factor for OSA (Mannarino *et al.,* 2012; Karl *et al.,* 2015).

Several studies showed that there is an adipose accumulation around the upper airway of obese subjects causing it to become narrower and easily collapse. In other words, adipose accumulation increases the mechanical load in the upper airway causing air flow obstruction during sleep. The neuromuscular response to open the airway as compensation for air obstruction is also known to be disturbed in obese subjects (Schwartz *et al.,* 2008).

There were no differences in OSA risk levels between men and women in this study. In contrast, several studies showed the prevalence of OSA was higher in men than in women (Karl *et al.,* 2015; Senaratna *et al.,* 2017). Other studies also showed that men have higher AHI than women (Gabbay & Lavie, 2012). These differences are caused by adipose distribution between men and women. Adipose accumulation in obese men tends to distributed in the upper body parts and trunk, including the tongue, soft palate, and lateral pharynx wall. In contrast to obese women, adipose accumulation is distributed in the extremities and lower body parts. Adipose accumulation around the pharynx increases extraluminal pressure so that pharynx tends to collapse (Wimms *et al.,* 2016). The compensatory mechanism by the pharynx dilator muscle to maintain airway patency is controlled through a reflex mechanism that originates from a chemoreceptor and is influenced by sex hormones (Mannarino *et al.,* 2012). In men, the response to hypoxia is lower during sleep, whereas in women the response is the same between sleep and wakefulness. Besides, an increase in obesity in women is offset by improvements in chemosensitivity responses to hypoxia and

hypercapnia. Thus, women are more able to maintain the patency of their airways during sleep than men (Wimms *et al.,* 2016).

The average neck circumference in this study showed that subjects with high risk for OSA had a greater neck circumference compared to subjects with low risk for OSA. Other studies have shown a significant relationship between neck circumference and OSA in both obese and non-obese patients, but no significant association was found between BMI and the incidence of OSA in ischemic stroke patients (Anwar *et al.,* 2017). This is in line with research conducted in 219 OSA subjects in Japan. It was proven that the ratio of neck/height circumference had a stronger correlation with OSA severity than neck circumference or BMI alone (Kawaguchi *et al.,* 2011). Other studies suggest that the ratio of the neck and large tonsil circumference can be used as a screening for subjects aged 8-18 years with a high-risk for OSA (Narang *et al.,* 2018).

Table 3. Effect of OSA Risk Levels on Cognitive Function

The risk level for OSA	Cognitive Function				Total		P	OR (95% CI)
	Disturbed		Normal					
	n	%	N	%	N	%		
High	20	90.91	2	9.09	22	100	0.001	12.727 (2.434-66.550)
Low	11	44	14	56	25	100		

The Chi-Square test results showed that there is a relationship between OSA risk level and cognitive function with Odds Ratio of 12.727 (Table 3). This means that subjects with a high-risk for OSA have 12.727 times greater chances to experience cognitive impairment compared to subjects with low-risk for OSA.

These study results are supported by the research that showed subjects with OSA experience significant cognitive impairment based on neurocognitive tests, including Troop Test (attention, information processing), Rey Auditory Verbal Learning Test (memory), Judgment of Line Orientation (spatial orientation), Trail-Making Test (attention, information processing), and Symbol Digit Modalities Test (alertness) (Arli *et al.,* 2015). Systematic and Meta-analytic review studies provide robust evidence that OSA impacts memory, attention and processing speed, and executive functions (Buck *et al.,* 2017). Research in Malaysia using the Mini-Mental Examination measured in 5 areas of cognitive functions comprising orientation, registration, attention and calculation, word recall and language abilities, and visuospatial also showed differences in cognitive function between subjects with severe OSA and subjects with moderate OSA (Yusop *et al.,* 2017).

Research using Diffusion Tensor Imaging showed a loss of gray matter in some brain parts of OSA subjects including the frontal and parietal cortex, temporal lobe, anterior cingulate, hippocampus and cerebellum (Macey *et al.,* 2012). Before being treated, it was known that there was a decrease in gray matter volume in the left hippocampus (entorhinal cortex), the left posterior parietal cortex, and the right superior frontal gyrus in OSA subjects. After treatment, there were

memory improvements, attention, and executive functioning that paralleled with gray matter volume increases in hippocampal and frontal structures (Canessa *et al.,* 2011).

Impaired cognitive function in OSA subjects begins with intermittent hypoxia. Furthermore, intermittent hypoxia results in endothelial dysfunction through oxidative stress, inflammation, and reduced NO availability (Atkeson & Jelic, 2008). Intermittent hypoxia and increased ROS disrupt endothelial Nitric Oxide Synthase (NOS) mRNA expression causing a decrease in nitrogen oxide production. In addition, intermittent hypoxia also causes mitochondrial stress which activates Nuclear Factor-KB to release inflammatory mediators such as, TNF-α, IL-6, and IL-8 that stimulate leukocyte aggregation as well as ICAM-1, UCAM-1, L-Selectin, and SE-selectin which stimulates leukocyte adhesion in blood vessels. Besides, inflammatory mediator C-reactive protein (CRP) is released, thus, directly inhibit nitric oxide synthase. This reaction triggers vasoconstriction and cerebral vascular endothelial damage (Daulatzai, 2012; Kerner & Roose, 2016). Vasoconstriction and damage to the endothelium causes a decline in cognitive function in the form of decreased memory, executive function, visuospatial disorders, and decreased attention caused by damage to neurons in the processing of thought, namely the prefrontal cortex (CPF) and limbic system (Daulatzai, 2012). People with OSA are also known to experience endothelial dysfunction that causes damage to the blood-brain barrier (BBB). The BBB disruption which is uniquely structured to tightly maintain homeostasis in the brain leads to changes in the microenvironment and affects synaptic plasticity, neuronal damage, a neurogenerative process leading to cognitive impairment (Lim & Pack, 2014; Kerner & Roose, 2016).

Therapy using continuous positive airway pressure (CPAP) is known to improve cognitive function in OSA patients. However, not all cognitive functions can return to normal after the therapy (Ferini-Stambi *et al.,* 2003). Based on the comparison of neurocognitive tests between subjects with OSA and subjects who only snore (simple snoring), a decrease in cognitive function only occurs in subjects with OSA (Arli *et al.,* 2015). Therefore, subjects with a high-risk for OSA are advised to perform a polysomnographic evaluation. If they diagnosed with OSA, they should be treated to improve and prevent further decline in cognitive function.

The study results showed that with a 10% increase in body weight, the risk of OSA is increased by six times (Mannarino *et al.,* 2012). It is interesting to know the effect of weight loss on the risk for OSA and cognitive function, especially in subjects with obesity who are still in school.

CONCLUSION

A total of 25 subjects were at low risk for OSA and 22 subjects were at high risk for OSA. There were differences in BMI and neck circumference between high-risk and low-risk subjects for OSA. The risk for OSA was significantly associated with cognitive function. ($p = 0.001$; OR =12.727).

Considering the research subject are students with a high risk for OSA, the subjects are recommended to lose weight and do a polysomnographic examination. If based on polysomnographic examinations the student is diagnosed with OSA, the student should carry out management according to the doctor's recommendations to improve and prevent further cognitive decline. The effect of weight loss on cognitive function in subjects with high-risk for OSA should be explored in future studies.

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