

Research Article

Relationship of Invasive and Non-Invasive Tear Break Up Time in University Adult with Risk of Sleep Apnea

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Abstract

To evaluate Tear Break Up Time (TBUT) and Non-Invasive Tear Break Up Time (NIBUT) in those with the risk of Obstructive Sleep Apnea Syndrome (OSAS) based on Berlin questionnaire in a university population. Out of 113 studied subjects, 28.22% were at high risk of OSAS. The low risk of OSAS had mean TBUT and NIBUT of 6.64 ± 2.65 seconds and 8.47 ± 3.76 seconds respectively, and the high risk of OSAS had TBUT and NIBUT of 6.39 ± 3.74 seconds and 7.93 ± 4.25 seconds respectively. There was no statistically significant of TBUT ($p=0.256$) and NIBUT ($p=0.29$) between the two groups. The study shows a higher prevalence for high risk of OSAS in the studied population, with normal the tear film stability.

Keywords: Invasive tear break up time; Non-invasive tear break up time; Obstructive sleep apnea syndrome

Introduction

Obstructive Sleep Apnea (OSA) is a common disorder, characterized by sleep induced upper airway narrowing leading to symptomatic sleep disturbance. OSA leads to hypoxia in several tissues and associates with ocular diseases like glaucoma, optic neuropathy, papilledema, ptosis, ectropion, trichiasis, floppy eyelid syndrome, dry eye and punctate epithelial keratopathy [1-6]. The clinical examination of a tear film stability is essential when assessing the health and maintenance of the ocular surface in the clinical care of dry eye disease.

OSA can be calculated by different valid tools such as Polysomnography, Nocturnal pulse oximetry, and Berlin Questionnaire [7-9]. This study uses the Berlin Questionnaire to identify the subjects at risk for OSA in Malaysian University population. It is a self-report instrument that is focused on a set of known symptoms and clinical features associated with sleep apnea. In case of young individual, especially of university population, with a busy lifestyle and unmet sleep needs may increase the risk of having obstructive sleep apnea and the OSA leads to affect the tear physiology [6,10]. This study has focused on student group to identify the rate of risk for OSA on them, and their tear film stability.

Materials and Methods

This was a prospective cross-sectional study of subjects (20-39 years), carried out in Twintech International University College of Technology, Faculty of optometry, Kuala Lumpur, Malaysia. The informed consent form was taken from each individual. Subjects for this study were the Malaysian students of Twintech International University College of Technology. Individuals who expressed their interest to participate and satisfied the inclusion criteria were considered for this study. All individuals satisfied the inclusion criteria set for this study as follow: age 20 to 39 years, no current medication, no contact lens wear, no history of any ocular surgery, visual acuity of 6/9 or better, normal appearance of all corneal layers

in on slit lamp examination and no corneal lesions. Those who were unable to read or understand English, individuals who were not willing to participate in this research and those with current illness except hypertension were all excluded.

Habitual visual acuity was measured using a Snellen chart. Then, each subject underwent an interview for Berlin Questionnaire, and clinically tested for his/her tear film stability that included Non-Invasive Tear Break Up Time (NITBUT) and Tear Break Up Time (TBUT).

The Non-Invasive Tear Break-Up Time (NIBUT) test measures tear stability without the introduction of a foreign substance into the tear film [11]. The non-NIBUT was assessed by using Bausch and Lomb keratometer with Shin-Nippon S0-21. The subject was seated carefully and the keratometer was then well adjusted and focused on the right eye with the mires in focus, the subject was asked to blink once and to refrain from blinking. A stopwatch was started after the last complete blink. At the first sign of any distortion of the mires, the stopwatch was stopped and the time noted. If the subject blinks between measurements, the test was halted, and then repeated after several blinks. The time interval between the last blink and the first sign of mire distortion was recorded in seconds as the NIBUT. The test was repeated for three times to increase the reliability and the average was taken [12].

Tear break-up time is the time needed after blinking of the fluorescein treated eye for the appearance of dark spots in the fluorescence of the tear film [13,14]. For the measurement of TBUT, the upper eyelid of the right eye was slightly lifted and the fluorescein strip was then used to stain the eye. The subject was asked to blink a few times without squeezing for homogenous mixing of fluorescein in the tear film. Then, the tear film was observed by using a cobalt-blue filter. The stopwatch was started after the last blink and the appearance of dry spots on the corneal surface was detected and recorded in seconds. Average of three readings were taken. Berlin Questionnaire involves three categories related to the risk of having

sleep apnea. It consists of questions on the symptoms such as snoring, tiredness, and their frequency. The questionnaire also includes the history of high blood pressure. Body Mass Index (BMI) was calculated for all the individuals. Finally, grouping for high risk and lower risk for OSAS were classified from their overall scores [15,16]. If the score is positive for 2 or more categories was considered as high risk and if there is only 1 or no categories has a positive score was included in low risk for OSAS.

Statistical analysis

Statistical analyses were done by using SPSS version 16.0 statistical software and MS Excel 2007. Test of normality was performed by Kolmogorov- Smirnov test. Mann-Whitney test was performed between the high and low-risk groups of OSAS. The age, sleeping hour, height, and BMI were compared with the two risk group of OSAS and also with the gender. A p-value of ≤ 0.05 was set for statistically significant.

Results

Of the total 113 subjects in this research, there were (40 males and 73 females) with a mean age of 23.03 ± 3.21 years. Males had a mean age of 24.88 ± 4.29 years and the females had a mean age of 22.01 ± 1.78 years. The mean BMI of the total population was 23.45 ± 5.91 with a mean height of 1.64 ± 0.13 m and weight of 62.81 ± 18.86 kg. The average sleeping hour was 6.22 ± 1.52 hours with a range of 3-10 hours. There were 32 subjects (28.32%) were at high risk of Obstructive Sleep Apnea Syndrome (OSAS) according to the Berlin questionnaire. Out of them, 17 (32.5%) were male and 15 (20%) were female (Table 1).

This study reported that 33 (29.2%) respondents (13 males and 20 females) reported snoring out of the 113 respondents. The presence of snoring was found to be more prevalent in individuals of high-risk of OSA with 59.4%. The presence of snoring of 3-4 times a week or more including both risk groups was reported as 42.4% whereas, 18.2% reported that their snoring was louder than talking or very loud and 30.3% admitted that their snoring bothers others. Total of 18.2% reported witnessed pauses in breathing while asleep in the same subgroup.

The mean tear Break Up Time (TBUT) and Non-Invasive Break Up Time (NIBUT) of this study were 6.57 ± 2.99 seconds and 8.32 ± 3.90 seconds respectively. Low risk and high risk of OSAS had the mean TBUT of 6.64 ± 2.65 seconds and 6.39 ± 3.74 seconds respectively and NIBUT of 8.47 ± 3.76 seconds and 7.93 ± 4.25 seconds respectively (Table 1).

In the Mann-Whitney test, the age ($p=0.62$) and sleeping hour ($p=0.85$) were not statistically significant between the two risk group of OSAS. There was also no significant difference in TBUT ($p=0.256$) and NIBUT ($p=0.29$) in the high and low risk of OSAS. Others variables like height ($p=0.037$), weight ($p \leq 0.001$) and BMI ($p \leq 0.001$) were statistically significant between the risk groups. Using the gender as the variable; the age ($p \leq 0.001$), height ($p \leq 0.001$), weight ($p \leq 0.001$), and BMI ($p=0.14$) were statistically significant. The sleeping hour ($p=0.061$), TBUT ($p=0.051$) and NIBUT ($p=0.39$) were not statistically significant (Table 1).

A Spearman correlation was computed to assess the relationship

Table 1: Baseline characteristics of the study population.

Characteristics	Mean \pm S.D	P-value
Age in years	23.03 \pm 3.21	
Male	24.88 \pm 4.27	0.001
Female	22.01 \pm 1.78	
High-Risk Group	23.59 \pm 4.19	0.621
Low-Risk Group	22.80 \pm 2.73	
Height in meters	1.64 \pm 0.13	
Male	1.70 \pm 0.09	0.001
Female	1.60 \pm 0.14	
High-Risk Group	1.66 \pm 0.10	0.037
Low-Risk Group	1.63 \pm 0.14	
Weight in kilograms	62.81 \pm 18.86	
Male	74.49 \pm 22.71	0.001
Female	56.42 \pm 12.51	
High-Risk Group	79.89 \pm 23.82	0.001
Low-Risk Group	56.07 \pm 10.73	
BMI in S.I units (kg/m ²)	23.45 \pm 5.91	
Male	25.64 \pm 7.08	0.014
Female	22.25 \pm 4.81	
High-Risk Group	28.93 \pm 7.28	0.001
Low-Risk Group	21.41 \pm 3.02	
TBUT in seconds	6.57 \pm 2.99	
Male	5.79 \pm 2.41	0.051
Female	7.00 \pm 3.20	
High-Risk Group	6.39 \pm 3.74	0.256
Low-Risk Group	6.64 \pm 2.65	
NIBUT in seconds	8.32 \pm 3.9	
Male	7.84 \pm 3.42	0.39
Female	8.58 \pm 4.13	
High-Risk Group	7.93 \pm 4.25	0.29
Low-Risk Group	8.47 \pm 3.76	
Sleeping hours in hours	6.22 \pm 1.52	
Male	5.88 \pm 1.84	0.061
Female	6.41 \pm 1.28	
High-Risk Group	6.19 \pm 1.72	0.85
Low-Risk Group	6.23 \pm 1.44	

between tear break up time, sleeping hour, body mass index and age. There was a weak negative correlation between tear break up time with sleeping hour ($r=-0.086$, $p=0.366$), body mass index ($r=-0.042$, $p=0.658$) and not significant statistically. There was also a weak positive correlation between TBUT with age ($r=0.059$, $p=0.535$). The non-invasive tear break up time and sleeping hour had a positive relationship, $r=0.054$, $p=0.573$. But the non-invasive tear break up time with body mass index ($r=-0.227$, $p=0.16$) and age ($r=-0.018$, $p=0.847$) had a negative relationship. There was no significant correlation between TBUT and NIBUT with sleeping hour ($r=-0.086$, $p=0.366$) ($r=0.054$, $p=0.573$) respectively.

There was a prevalence of 6 (5.3%) individuals who reported that they have hypertension. The high-risk group has 15.6% who have hypertension compared to the low-risk group who only have 1.2%.

Sleepiness and tiredness were common in this study population. Forty-three out of the 113 respondent, they reported that they feel sleepy when they woke up in the morning greater than 3-4 times a week or more. Out of the total population of 113, 42 (37.2%) had felt tired during a waking time more than 3-4 per week. There was about 17.7% person who reported that they had fallen asleep while driving at least once in their lifetime.

Discussion

Patient with OSAS has been identified using the Berlin questionnaire, has been used as the screening tools [15,16]. It has been previously employed in similar primary care settings [8,16]. The Berlin questionnaire is an instrument validated to determine the prevalence of OSA in both the western population and Asian population [17-20].

Studies done in the United States and Europe by using the Berlin questionnaire had reported a 26% prevalence estimate of high risk for OSAS; with a mean age of 49 years old [8,21]. Study done in a Pakistani population has a prevalence of 10% with the mean age of 30.4 years [22]. Our study results showed 28.32% prevalence of high risk of OSAS with a mean age of 29 years old in Malaysian. This study reports the higher prevalence of having a higher risk of OSAS as compared to the previous study. It may be a finding that suggests younger aged students are more prone to have OSAS. The difference in the prevalence may also be caused by the different age group that was included in studies.

Both TBUT and NIBUT provide the tear film stability, and the measurement of tear film stability is important while assessing the ocular surface in case of dry eye syndrome. Dry eye syndrome and tear film dysfunction are synonymous. The previous report suggests that OSAS causes tear film dysfunction, this leads to ocular complications such as excessive tearing, corneal surface damage, and vision changes [6,23,24]. The present study showed that the mean TBUT and NIBUT values were lower in high risk of OSAS group as compared to the low risk of OSAS group, although the difference of TBUT and NIBUT values were not statistically significant, as well as may not have clinical significance. The mean difference of TBUT and NIBUT values were 0.26 sec and 0.55 sec respectively. Based on this result, it suggests that increased in severity of OSAS or long term of OSAS may lead to tear film dysfunction, and age can also be the potential risk factor.

In this study, there was no significant difference in NIBUT and TBUT between males and females. This is in agreement with many earlier studies [25-30].

Our data showed that the risk of OSAS was higher in male (42.5%) as compared to female (20.5%), suggesting similar results to the earlier studies both in American and European, and Asian subjects [8,9,15,31-33]. This difference between male and female as a result in differences in the distribution of adipose tissue, upper-airway anatomy and muscle function, control of ventilation, and the effects of sex hormones and leptin [34].

The main factor contributing to the development of OSAS in our

modern societies is the increase in obesity. This reports showed higher mean BMI in subjects having a higher risk of OSAS. Increased in BMI is one of the major factors that lead to sleeping disorder [31,35-37].

In this study, 29.2% (mean age of 30.4 years) of an individual had a prevalence of snoring, which is similar to previous reports in an Asian population. The prevalence of snoring in the Pakistani and Indian population was 24.9% (mean age of 30.4 years) and 26% (mean age of 47.84 years) respectively [20,22]. However, the US population had a higher prevalence of snoring which was reported as 52-54% and the mean age of the studied population was 49 years old. This suggests that western population has more likely higher prevalence of snoring as compared with Asian population [16,21]. Previous studies suggest that various vascular diseases such as hypertension, ischemic heart disease, and cerebrovascular accident have been associated with snoring [38-42]. However, age and obesity are the major confounding risk factors to lead those changes.

According to the National Sleep Foundation, they suggest sleeping hour between 7-9 hours per night is essential to perform daily tasks. The mean sleeping hour of this study subjects was 6.22 ± 1.52 hours, and similar to the previous report on medical student in International Medical University Malaysia had a mean sleeping hour of 6.6 ± 1.3 [43]. Previous reports suggest students are exposed to a lot of pressure due to academic demands and lead to sleep disturbance insufficient sleep duration, delayed sleep onset, and occurrence of napping episodes during the daytime [44-47].

Poorer general health and car crashes are linked to sleepiness, suggesting the prevalence of drowsy driving among respondent is higher among the high risk of OSAS groups [48,49]. This is an important public health hazard and this particular need an attention as it may put many drivers in the greater risk of road traffic accidents [50].

Limitation

Our study has certain limitations to be considered. The Berlin questionnaire is not particularly validated for Malaysian population and not a gold standard tool for the diagnosis of OSAS, though Berlin questionnaire has a good specificity and sensitivity to identify individuals at the risk for OSAS. Sleep apnea may not only affect the tear stability but also the tear quality and volume, so it is important to measure all the parameter. Although the same room was maintained for whole data collection, temperature and humidity were not measured, these variables could have an effect on tear film measurements.

Conclusion

Based on this study, there is reduced sleeping hours among university individuals and has a higher prevalence for high risk of OSAS in the studied population, with normal the tear film stability. Berlin questionnaire is essential in younger age group individuals, can be easily performed during a general/ ocular examination.

References

1. Mojon DS, Hess CW, Goldblum D, Fleischhauer J, Koerner F, Bassetti C, et al. High prevalence of glaucoma in patients with sleep apnea syndrome. *Ophthalmology*. 1999; 106: 1009-1012.
2. Mojon DS, Mathis J, Zulauf M, Koerner F, Hess CW. Optic neuropathy

- associated with sleep apnea syndrome. *Ophthalmology*. 1998; 105: 874-877.
3. Purvin VA, Kawasaki A, Yee RD. Papilledema and obstructive sleep apnea syndrome. *Arch Ophthalmol*. 2000; 118: 1626-1630.
 4. Mojon DS, Goldblum D, Fleischhauer J, Chiou AG, Frueh BE, Hess CW, et al. Eyelid, conjunctival, and corneal findings in sleep apnea syndrome. *Ophthalmology*. 1999; 106: 1182-1185.
 5. McNab AA. Reversal of floppy eyelid syndrome with treatment of obstructive sleep apnoea. *Clin Experiment Ophthalmol*. 2000; 28: 125-126.
 6. Hirunwiwatkula P, Puangsricharerna V, Sothornwita N, Pongpun RP, Sawatdiwithayayong J. Eye diseases associated with obstructive sleep apnea syndrome in an Asian population. *Asian Biomedicine*. 2010; 4: 645-650.
 7. Chiner E, Signes-Costa J, Arriero JM, Marco J, Fuentes I, Sergado A. Nocturnal oximetry for the diagnosis of the sleep apnoea hypopnoea syndrome: a method to reduce the number of polysomnographies?. *Thorax*. 1999; 54: 968-971.
 8. Netzer NC, Hoegel JJ, Loube D, Netzer CM, Hay B, Alvarez-Sala R, et al. Prevalence of symptoms and risk of sleep apnea in primary care. *Chest*. 2003; 124: 1406-1414.
 9. Sharma SK, Vasudev C, Sinha S, Banga A, Pandey RM, Handa KK. Validation of the modified Berlin questionnaire to identify patients at risk for the obstructive sleep apnoea syndrome. *The Indian journal of medical research*. 2006; 124: 281-290.
 10. Bixler EO, Vgontzas AN, Lin HM, Calhoun SL, Vela-Bueno A, Kales EDS. Role of Obesity, Diabetes, and Depression. *J Clin Endocrinol Metab*. 2005; 90: 4510-4515.
 11. Mengher LS, Bron AJ, Tonge SR, Gilbert DJ. A non-invasive instrument for clinical assessment of the precorneal tear stability. *Cum Eye Res*. 1985; 4: 1-7.
 12. Cho P. Reliability of a portable noninvasive tear break-up time test on Hong Kong-Chinese. *Optom Vis Sci*. 1993; 70: 1049-1054.
 13. Norn MS. Semi-quantitative interference study of fatty layer of pre-corneal film. *Acta Ophthalmology*. 1979; 57: 766-774.
 14. Lemp MA, Hamill JR. Factors affecting tear film break up in normal eyes. *Arch Ophthalmol*. 1973; 89: 103-105.
 15. Ip MS, Lam B, Tang LC, Lauder IJ, Ip TY, Lam WK. A community study of sleep-disordered breathing in middle-aged Chinese women in Hong Kong: prevalence and gender differences. *Chest*. 2004; 125: 127-134.
 16. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med*. 1999; 131: 485-491.
 17. Marin JM, Gascon JM, Carrizo S, Gispert J. Prevalence of sleep apnoea syndrome in the Spanish adult population. *Int J Epidemiol*. 1997; 26: 381-386.
 18. Olson LG, King MT, Hensley MJ, Saunders NA. A community study of snoring and sleep disordered breathing. Prevalence. *Am J Respir Crit Care Med*. 1995; 152: 711-716.
 19. Ohayon MM, Guilleminault C, Priest RG, Caulet M. Snoring and breathing pauses during sleep: telephone interview survey of a United Kingdom population sample. *BMJ*. 1997; 314: 860-863.
 20. Udawadia ZF, Doshi AV, Lonkar SG, Singh CI. Prevalence of sleep disordered breathing and sleep apnea in middle-aged urban Indian men. *American journal of respiratory and critical care medicine*. 2004; 169: 168-173.
 21. Hiestand DM, Britz P, Goldman M, Phillips B. Prevalence of symptoms and risk of sleep apnea in the US population: Results from the national sleep foundation sleep in America 2005 poll. *Chest*. 2006; 130: 780-786.
 22. Taj F, Aly Z, Kassi M, Ahmed M. Identifying people at high risk for developing Sleep Apnea Syndrome (SAS): a cross-sectional study in a Pakistani population. *BMC Neurology*. 2008; 8: 50.
 23. Johnson ME, Murphy PJ. Changes in the tear film and ocular surface from dry eye syndrome. *Prog Retin Eye Res*. 2004; 23: 449-474.
 24. Perry HD. Dry eye disease: pathophysiology, classification, and diagnosis. *Am J Manag Care*. 2008; 14: S79-S87.
 25. Mohidin N, Bay TC, Yap M. Non-invasive tear break-up time in normal Malays. *Clin Exp Optom*. 2002; 85: 1: 37-41.
 26. Lemp MA, Hamill JR. Factors affecting tear film breakup in normal eyes. *Arch Ophthalmol*. 1973; 89: 103-105.
 27. Chopra SK, George S, Daniel R. Tear film Break Up Time (BUT) in contact lens wearers and contact lens wearers in normal Indian population. *Indian J Ophthalmol*. 1985; 33: 213-216.
 28. Amaechi OU, Osunwoke CM. The relation between invasive and non-invasive tear break up time in young adult. *JNOA*. 2004; 11: 29-32.
 29. Cho P. Reliability of a portable noninvasive tear break-up time test on Hong Kong-Chinese. *Optom Vis Sci*. 1993; 70: 1049-1054.
 30. Patel S, Virhia SK, Farrell. Stability of the precorneal tear film in the Chinese, African, Indian, Caucasian eyes. *Optom Vis Sci*. 1995; 72: 911-915.
 31. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badur S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med*. 1993; 328: 1230-1205.
 32. Block AJ, Boysen PG, Wynne JW, Hunt LA. Sleep apnea, hypopnea and oxygen desaturation in normal subjects. A strong male predominance. *N Engl J Med*. 1979; 300: 513-517.
 33. Kim J, In K, Kim J, You S, Kang K, Shim J, et al. Prevalence of sleep-disordered breathing in middle-aged Korean men and women. *Am J Respir Crit Care Med*. 2004; 170: 1108-1113.
 34. Kapsimalis F, Kryger MH. Gender and obstructive sleep apnea syndrome: part 2. Mechanisms. *Sleep*. 2002; 25: 499-506.
 35. Kripke DF, Ancoli-Israel S, Klauber MR, Wingard DL, Mason WJ, Mullaney DJ. Prevalence of sleep-disordered breathing in ages 40-64 years: a population based survey. *Sleep*. 1997; 20: 65-76.
 36. Richman RM, Elliott LM, Burns CM, Bearpark HM, Steinbeck KS, Caterson ID. The prevalence of obstructive sleep apnoea in an obese female population. *Int J Obes Relat Metab Disord*. 1994; 18: 173-177.
 37. Resta O, Foschino-Barbaro MP, Legari G, Talamo S, Bonfitto P, Palumbo A, et al. Sleep-related breathing disorders, loud snoring and excessive daytime sleepiness in obese subjects. *Int J Obes Relat Metab Disord*. 2001; 25: 669-675.
 38. Koskenvuo M, Kaprio J, Partinen M, Langinvainio H, Sarna S, Heikkilä K. Snoring as a risk factor for hypertension and angina pectoris. *Lancet*. 1985; 1: 893-896.
 39. Partinen M, Palomaki H. Snoring and cerebral infarction. *Lancet*. 1985; 2: 1325-1326.
 40. Koskenvuo M, Kaprio J, Telakivi T, Partinen M, Heikkilä K, Sarna S. Snoring as a risk factor for ischemic heart disease and stroke in men. *Br Med J*. 1987; 294: 16-19.
 41. Ayas NT, White DP, Manson JE, Stampfer MJ, Speizer FE, Malhotra A, et al. A prospective study of sleep duration and coronary heart disease in women. *Arch Intern Med*. 2003; 163: 205-209.
 42. Spiegel K, Leproult R, Van-Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet*. 1999; 354: 1435-1439.
 43. Zailinawati AH, Teng CL, Chung YC, Teow TL, Lee PN, Jagmohani KS. Daytime sleepiness and sleep quality among Malaysian medical students. *Med J Malaysia*. 2009; 64: 108-110.
 44. Abdulghani HM, Alrowais NA, Bin-Saad NS, Al-Subaie NM, Haji AM, Alhaqwi AI. Sleep disorder among medical students: Relationship to their academic performance. *Medical Teacher*. 2012; 34: S37-S41.
 45. Bahammam AS, Alaseem AM, Alzakri AA, Almeneessier AS, Sharif MM. The relationship between sleep and wake habits and academic performance in medical students: a cross-sectional study. *BMC Med Educ*. 2012; 12: 61.
 46. Rodrigues RND, Viegas SCAA, Esilva AAA, Tavares P. Daytime sleepiness

- academic performance in medical students. *Avg Neuropsychiatr.* 2002; 60: 6-11.
47. Ng EP, Ng Dk, Chan CH. Sleep duration, wake/sleep symptoms, and academic performance in Hong Kong Secondary School Children. *Sleep Breath.* 2009; 13: 357-367.
48. Briones, B, Adams N, Strauss M, Rosenberg C, Whalen C, Carskadon M, et al. Relationship between sleepiness and general health status. *Sleep.* 1996; 19: 583-538.
49. Lyznicki JM, Doege TC, Davis RM, Williams MA. Sleepiness, driving, and motor vehicle crashes. Council on Scientific Affairs, American Medical Association. *JAMA.* 1998; 279: 1908-1913.
50. Teran-Santos J, Jimenez-Gomez A, Cordero-Guevara J. The association between sleep apnea and the risk of traffic accidents. Cooperative Group Burgos-Santander. *N Engl J Med.* 1999; 340: 847-851.