Association between sleep parameters and metabolic syndrome among healthy middle-aged Koreans

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Association between sleep parameters and metabolic syndrome among healthy middle-aged Koreans

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ABSTRACT

Association between sleep parameters and metabolic syndrome among healthy middle-aged Koreans

BACKGROUND:

Sleep has been recognized as one of the important factors related to various health problems. Several studies have reported that sleep status affects the morbidity of metabolic syndrome; however, there are limited studies, particularly in Korea. Thus, the current study evaluates the association of sleep parameters including sleep duration, difficulty in sleep initiation, and obstructive sleep apnea (OSA) risk with metabolic syndrome in healthy middle-aged Koreans.

METHODS:

This study used data from 1,659 participants (588 of male and 1,071 of female) aged 30 to 64 years enrolled in the Cardiovascular and Metabolic diseases Etiology Research Center (CMERC) study conducted between 2013 and 2014. Multiple logistic regression models were used to examine the associations between sleep parameters and metabolic syndrome.

RESULTS:

Male participants with short sleep duration exhibited 3.41 times higher odds (95% confidence interval (CI) 1.40-8.28) of having metabolic syndrome after adjusting for age, body mass index, smoking status, drinking status, physical activity, depression, and risk

of OSA. On the other hand, female participants with difficulty in sleep initiation for 1–4 days/week were at higher risk for metabolic syndrome (adjusted odds ratio (OR) 1.75; 95% CI 1.06–2.89) than those without difficulty in sleep initiation. People with short sleep duration and difficulty in sleep initiation had a higher risk of metabolic syndrome (adjusted OR 4.94; 95% CI 1.05–23.21 in males, 2.23; 95% CI 1.01–4.94 in females) than those with intermediate sleep duration and no difficulty in sleep initiation. Corresponding OR for people with short sleep duration and no difficulty in sleep initiation was 3.34 (95% CI 1.15–9.67) in males, 1.36 (95% CI 0.50–3.72) in females. The high risk of OSA group exhibited an increased risk of abdominal obesity with an adjusted OR of 3.61 (95% CI 2.76–4.71) and high blood pressure with an OR of 2.39 (95% CI 1.82–3.14) compared to the low risk of OSA group.

CONCLUSION:

Our study suggested that short sleep duration and difficulty in sleep initiation are associated with metabolic syndrome among healthy middle-aged Koreans. The results of our study also imply that it is important to assess the quantitative and qualitative aspects of sleep. In addition, the high risk of OSA group was associated with components of abdominal obesity and high blood pressure. However, considering the indicators for determining the risk of OSA, including body mass index and diagnosed hypertension, caution is needed in interpretation.

Keywords: sleep, metabolic syndrome, healthy, middle-aged, Korean

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(Directed by Professor Hyeon Chang Kim)

I. INTRODUCTION

1. Background

Sleep has been recognized as one of the crucial factors influencing various health problems. With modernization, characterized by the widespread use of electricity, human sleep patterns have been changed. Modern life comes with an increased demand for high

performance at work, increased shift work, prolonged commuting times, and multiple leisure time activities (Centers for Disease and Prevention, 2011; Krueger &Friedman, 2009; Schoenborn &Adams, 2010). Generally, the proper sleep duration is about 7 to 8 hours in healthy adults (Ayas et al., 2003; Heslop et al., 2002). However, recently, sleep duration has decreased across the globe. The average self-reported sleep duration has decreased from over 8 hours in the 1960s to about 6.5 hours in 2012, with 20 to 30% of middle-aged Americans reporting a sleep duration of less than 6 hours (Centers for Disease and Prevention, 2011; Krueger &Friedman, 2009). Similar patterns have been reported in Asian populations (Shankar et al., 2008; Tamakoshi et al., 2004). According to the sixth Korea National Health and Nutrition Examination Survey (KNHANES-Ⅵ) 2013, the daily average sleep duration was 6.7 hours in Korean adults. About 15.3% of those who responded stated that their daily average sleep duration was less than 6 hours (Korea Centers for Disease Control and Prevention, 2013). Moreover, Koreans' average sleep duration is the shortest among the Organization for Economic Cooperation and Development (OECD) countries (OECD, 2011).

Several studies have reported that sleep duration is associated with obesity, diabetes, hypertension, atherosclerosis, and cardiovascular diseases (Ayas et al., 2003; Gottlieb et al., 2006; Taheri et al., 2004; Wolff et al., 2008; Yaggi et al., 2006). Moreover, short and long sleep durations have been shown to be linked to an increased risk of metabolic syndrome (Hall et al., 2008;Stefani et al., 2013). As some contend that sleep assessments based only on duration are not enough, some studies have suggested that it is necessary to consider qualitative aspects to understand global sleep status (Doi et al., 2000; Kaneita et al., 2008). Actually, in recent years, accumulated evidence has shown that sleep parameters, including not only sleep duration but also sleep quality and sleep disorders,

are independently associated with an increased risk of metabolic syndrome (Hung et al., 2013; Jennings et al., 2007; Lee et al., 2013; Sasanabe et al., 2006).

Metabolic syndrome, which consists of a complex combination of abdominal obesity, hypertension, impaired glucose tolerance, and dyslipidemia, is a significant health problem around the world (Alberti et al., 2009; Ervin, 2009; Fernandez-Berges et al., 2012). This medical disorder increases the morbidity and mortality of cardiovascular diseases and stroke by increasing the risk of atherosclerosis (Kadota et al., 2007; Nigam et al., 2006; Tillin et al., 2006). To decrease the mortality and morbidity of cardiovascular diseases and stroke, it is important to prevent and/or improve their risk factors, including metabolic syndrome. Though various factors affecting metabolic syndrome have been studied (Kastorini et al., 2011; Lakka &Laaksonen, 2007; Park et al., 2003), adequate sleep quality and quantity have been suggested to play important roles in the normal functioning of daily metabolic and hormonal processes and appetite regulation (Van Cauter et al., 2008). In prospective observational studies, disturbed sleep has been related to both diabetes and cardiovascular disease and their risk factors (Roost &Nilsson, 2002). In experimental studies, sleep deprivation has been found to lower glucose tolerance and thyrotropin concentration, raise evening cortisol concentrations, and increase activity of the sympathetic nervous system, suggesting a neuroendocrine profile that may be conducive to full metabolic syndrome (Spiegel et al., 1999).

Obstructive sleep apnea (OSA) is characterized by repeated episodes of apnea and hypopnea during sleep. In addition, there is a growing body of evidence to support the belief that severe OSA is a risk factor for metabolic syndrome and cardiovascular diseases (Marshall et al., 2008; Somers et al., 2008; Young et al., 2008).

However, particularly in Korea, there have been limited studies; thus, they have not

provided sufficient evidence of the relation between sleep parameters and traditional indicators of metabolic impairments. Moreover, research reported in Korea has either considered only sleep duration (Stefani et al., 2013) or considered sleep duration and quality separately with relatively small numbers of subjects (Lee et al., 2013).

2. Objectives

This study evaluates the relationship of each of the sleep parameters including sleep duration, difficulty in sleep initiation, and OSA risk with metabolic syndrome in healthy middle-aged Koreans. We evaluated the prevalence of metabolic syndrome in healthy middle-aged Koreans according to self-reported sleep duration, difficulty in sleep initiation, and OSA risk. Moreover, we considered the combined effect of sleep duration and difficulty in sleep initiation, which may influence each other, on metabolic syndrome.

II. METHODS

1. Study population

This study used data from the Cardiovascular and Metabolic diseases Etiology Research Center (CMERC) study, an ongoing community-based cohort study. Over the course of five years, the CMERC study plans to recruit more than 4,000 participants relatively healthy middle-aged adults from urban and rural areas of South Korea. The CMERC study enrolled 1,663 participants aged 30 to 64 years in the 2013 and 2014 baseline examinations.

For the current analysis, we excluded two participants who had a history of stroke or myocardial infarction and two participants lacking information on fasting glucose level and waist circumference. Finally, 1,659 participants (588 male and 1,071 female) were analyzed to determine the association between sleep and metabolic syndrome. The final sample for the analyses of this study is outlined in Figure 1. All participants provided written informed consent, and the Institutional Review Board of Severance Hospital, Yonsei University College of Medicine, approved the study protocol.

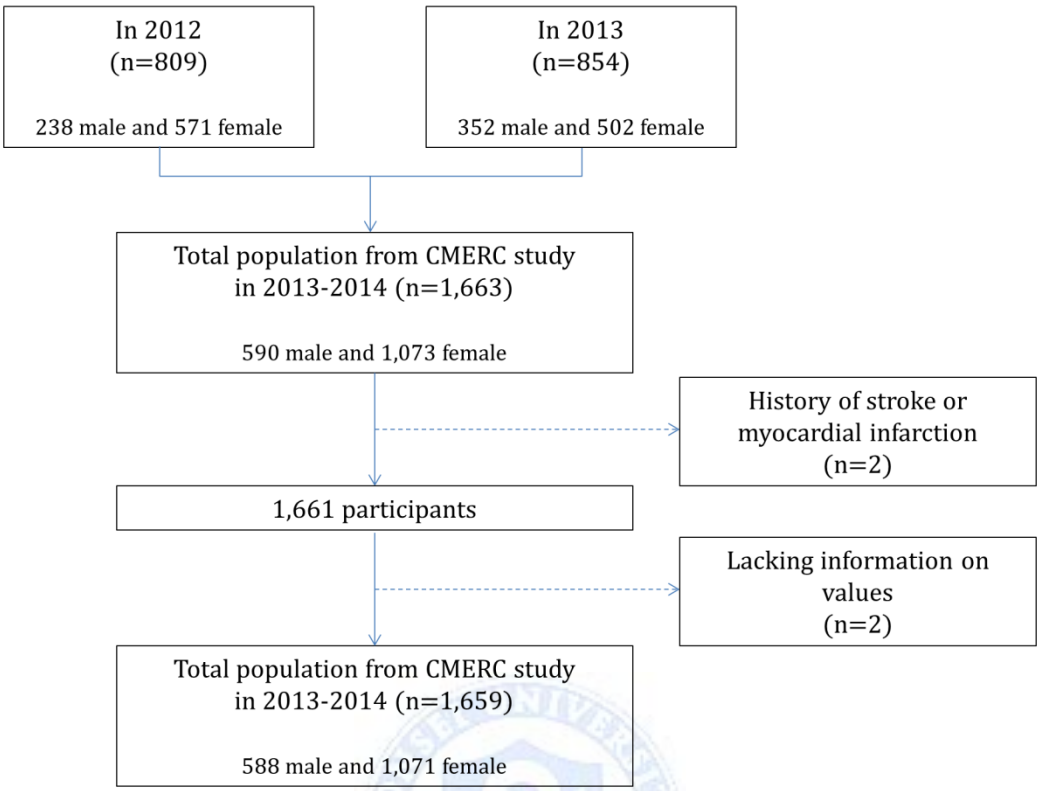

Figure 2. Flowchart of the selection of the final study population

2. Measurements

1) Assessment of sleep parameters

To investigate the study subjects' sleep duration, difficulty in sleep initiation, and OSA risk, we used self-report questionnaires. Sleep duration was assessed by self-reported responses to the question, "During the past year, how many hours have you usually slept each day (including naps)?" Responses were assigned to one of three subcategories: Short (≤5 hours), Intermediate (5–9 hours), Long (≥9 hours). Short or long sleep durations were defined according to the International Classification of Sleep Disorders definition (Ito &Inoue, 2015). Difficulty in sleep initiation was assessed by self-reported responses to the question, "Do you currently have a sleep initiation problem?" Responses were assigned to one of three subcategories: None, 1–4 days/week, 5+ days/week. To evaluate OSA risk, we used the Berlin Questionnaire, which includes three categories with ten questions: five questions related to snoring behaviors/witnessed apneas (Category 1), three about daytime sleepiness (Category 2), and two about the patient's history of hypertension and/or obesity (Category 3). Subjects were considered to be at a high risk for OSA if they had at least two of the following conditions: (1) Two positive answers to Category 1 questions that indicated the presence of persistent snoring (more than 3 times a week) with snoring sufficiently loud to be heard in the next room and/or persistent apnea (more than 3 times a week or everyday); (2) daytime sleepiness defined as ever falling asleep while driving or as feeling tired or fatigued after sleep and feeling tired or fatigued during wake time at least 3 days a week (Category 2); and (3) presence of hypertension or obesity. Subjects who denied chronic symptoms or had chronic symptoms or signs in only one category were classified as being at a low risk for OSA.

2) Assessment of metabolic syndrome

Metabolic syndrome was defined based on the National Cholesterol Education Program Adult Treatment Panel Ⅲ (NCEP-ATP Ⅲ) criteria. The presence of any three of the following five abnormalities constitutes a diagnosis of metabolic syndrome: (ⅰ) waist circumference > 90cm in males and >80 cm in females; (ⅱ) elevated triglycerides with fasting plasma triglycerides ≥150mg/dL; (ⅲ) low HDL cholesterol with fasting HDL cholesterol <40 mg/dL in males and <50 mg/dL in females; (ⅳ) elevated blood pressure with systolic blood pressure ≥130mmHg and/or diastolic blood pressure ≥85 mmHg and/or the use of BP-lowering medication; (ⅴ) elevated fasting plasma glucose with fasting plasma glucose ≥100 mg/dL and/or a diagnosis diabetes and/or the use of anti-diabetes medication.

Waist circumference was measured between the lower borders of the rib cage and iliac crest with a measuring tape (SECA-201; SECA, Hamburg, Germany). Blood pressure was measured three times at an interval of 2 minutes by an autonomic sphygmomanometer (Omron HEM-7080IC, Omron Healthcare Co., Ltd., Kyoto, Japan) on the right arm of the subject while sitting after taking at least five minutes of rest. The second and third measurements were averaged for analyses. Blood samples were collected from the antecubital vein after at least 8 hours of fasting. Enzymatic methods were applied to measure total cholesterol, HDL cholesterol, and triglyceride, and fasting blood glucose levels were measured by the colorimetry method with an Auto Analyzer (ADVIA 1800; Siemens Healthcare Diagnostic Inc., Deerfield, IL, USA).

3) Covariates

Age, sex, body mass index, smoking status, drinking status, physical activity and depression were considered as covariates in the present analyses. Age and body mass index were analyzed as continuous variables. Sex was categorized as male versus female. Smoking status was categorized into three groups: non-smoker, former smoker, and current smoker. Drinking status was categorized into three groups: non-drinker, former drinker, and current drinker. To assess physical activity level, we used self-reported data about the number of minutes spent in vigorous and moderately intense activity and walking during the last 7 days. We initially calculated the Metabolic Equivalents (METs)-minutes score by multiplying the number of minutes by 8 (vigorous), 4 (moderate), and 3.3 (walking) (Ainsworth, et al. 2000). Then, according to the Global Physical Activity Questionnaire (GPAQ) analysis framework, physical activity levels could be classified into low, moderate, or high intensity (WHO, 2004). To define depression, we used a Korean version of the Beck Depression Inventory-Ⅱ (BDI-Ⅱ) that has been validated in Korea (Song et al., 2012). Depression was defined as a BDI-Ⅱ score of 22 points or more. This cutoff value reflects clinical levels of depression in the Korean version of the BDI-Ⅱ with 94% sensitivity and 98% specificity (Seo &Park, 2015). Additionally, females were categorized by menopausal status.

3. Statistical analysis

Student's t-test and the chi square test were used to analyze the general characteristics of the study population by sex. Multiple logistic regression models were used to examine the independent associations between sleep parameters and metabolic syndrome. We fit logistic regression models to examine the relationship between sleep duration, difficulty in sleep initiation (respectively or as a combined exposure), and risk for sleep apnea. Overall, we applied the following serial models: age, sex-adjusted (Model 1); age, sex, body mass index, smoking status, drinking status, physical activity, depression-adjusted (Model 2); age, sex, body mass index, smoking status, drinking status, physical activity, depression, other sleep parameters-adjusted (Model 3). When stratifying by sex, the "sex" variable was excluded in all models. When analyzing females, menopausal status was additionally adjusted in Models 2 and 3. All analyses were performed using SAS version 9.2 (SAS Institute, Inc. Cary, NC), and statistical significance was defined as a two-sided p-value < 0.05.

III. RESULTS

1. Characteristics of the study population

Table 1 lists the general characteristics of the study population in overall, male, and female participants. Out of a total of 1,659 subjects, 588 (35.4%) were male. Overall, the subjects' mean age was 49.1 ± 9.7 years, and the mean body mass index was 23.7 ± 3.1kg/m². Manual workers were 16.2%, and non-manual workers were 51.2% of the total. Current smokers were 15.3%, and current drinkers were 66.1% of the total. The mean BDI-Ⅱ score was 10.1 ± 7.5, and those with depression were 8.5% of the total. Those performing high-intensity physical activity were 20.3%, and those performing moderate-intensity physical activity were 25.5%. Those with short and long sleep durations were 15.7% of the total (9.2% and 6.5%, respectively), and 27.7% of subjects had difficulty in sleep initiation. When divided by sex, both sexes showed significant differences in age, education level, occupation, marital status, smoking status, drinking status, BDI-Ⅱ score, depression, sleep duration, difficulty in sleep initiation, OSA risk, and metabolic syndrome components (p<0.05 for each). For body mass index, physical activity level did not differ in male and female subjects.

While 10.6% of females had metabolic syndrome, 21.0% of males met the criteria for metabolic syndrome. Among female subjects, the mean age was 50.1 ± 9.3 years, 10.8% had short sleep duration, 7.0% had long sleep duration, 31.6% had difficulty in sleep initiation, and 10.2% had depression, all of which were significantly higher than those in male subjects. On the other hand, male subjects were more likely current

smokers/drinkers and had a higher risk of OSA than females.

Table 1. General characteristics of study population

Variables	Total (n=1,659)	Male (n=588)	Female (n=1,071)	*p*-value
Age (years)	49.1 ± 9.7	47.3 ± 10.3	50.1 ± 9.3	0.0019
Body mass index (kg/m^2)	23.7 ± 3.1	24.6 ± 3.0	23.2 ± 3.0	0.7711
Education (n=1,658)				<.0001
Elementary or Middle school graduate	279 (16.8)	53 (9.0)	226 (21.1)	
High school graduate	609 (36.7)	176 (29.9)	433 (40.5)	
College or higher graduate	770 (46.4)	359 (61.1)	411 (38.4)	
Occupation				<.0001
Not employed	541 (32.6)	42 (7.1)	499 (46.6)	
Manual	269 (16.2)	135 (23.0)	134 (12.5)	
Non-manual	849 (51.2)	411 (69.9)	438 (40.1)	
Marital status				<.0001
Married	1,422 (85.7)	532 (90.5)	890 (83.1)	
Unmarried	237 (14.3)	56 (9.5)	181 (16.9)	
Smoking status				<.0001
Non-smoker	1,131 (68.2)	141 (24.0)	990 (92.4)	
Ex-smoker	275 (16.6)	236 (40.1)	39 (3.6)	
Current smoker	253 (15.3)	211 (35.9)	42 (3.9)	
Drinking status				<.0001
Non-drinker	487 (29.4)	64 (10.9)	423 (39.5)	
Ex-drinker	76 (4.6)	35 (6.0)	41 (3.8)	
Current drinker	1,096 (66.1)	489 (83.2)	607 (56.7)	
BDI-Ⅱ score	10.1 ± 7.5	8.7 ± 6.7	10.8 ± 7.8	<.0001
Depression (BDI-Ⅱ score ≥22)	141 (8.5)	32 (5.4)	109 (10.2)	0.0009
Physical activity level				0.1763
High intensity	332 (20.0)	130 (22.1)	202 (18.9)	
Moderate intensity	423 (25.5)	138 (23.5)	285 (26.6)	
Low intensity	904 (54.5)	320 (54.4)	584 (54.5)	
Sleep duration				0.0020
Short (≤ 5 hours)	152 (9.2)	36 (6.1)	116 (10.8)	
Intermediate (5–9 hours)	1,400 (84.4)	520 (88.4)	880 (82.2)	
Long (≥9 hours)	107 (6.5)	32 (5.5)	75 (7.0)	
Difficulty in sleep initiation				<.0001
None	1,201 (72.4)	469 (80.0)	732 (68.4)	
1–4days/week	321 (19.4)	85 (14.5)	236 (22.0)	
5+ days/week	137 (8.3)	34 (5.8)	103 (9.6)	
Obstructive sleep apnea				<.0001
Low risk	1,247 (75.2)	378 (64.3)	869 (81.1)	
High risk	412 (24.8)	210 (35.7)	202 (18.9)	
Metabolic syndrome components				
Abdominal obesity	384 (23.2)	172 (29.3)	212 (19.8)	<.0001
TG≥150mg/dL	379 (22.9)	212 (36.1)	167 (15.6)	<.0001
Low HDL-C	416 (25.1)	113 (19.2)	303 (25.0)	<.0001
Blood pressure ≥ 130/85 mmHg	513 (30.9)	245 (41.7)	268 (25.0)	<.0001
Fasting glucose ≥ 100 mg/dL	239 (15.1)	126 (21.4)	121 (11.3)	<.0001
Number of metabolic syndrome components				
0	630 (38.0)	166 (28.2)	464 (43.3)	<.0001
≥1	1,029 (62.0)	422 (71.8)	607 (56.7)	<.0001
≥2	528 (31.8)	243 (41.3)	285 (26.6)	<.0001
≥3 (Metabolic syndrome)	235 (14.2)	122 (20.7)	113 (10.6)	<.0001

Data were expressed as means ± standard deviation and number (%)

2. Association between sleep duration and metabolic syndrome

Table 2 shows the odds ratio (OR) and 95% confidence interval (CI) of sleep duration for metabolic syndrome in study subjects. The intermediate sleep duration (5–9hours) group was used as a reference category in the logistic regression model. Overall, the crude ORs of the short (≤5 hours) and long (≥9 hours) sleep duration groups for metabolic syndrome were 2.07 (95% CI 1.39–3.10) and 0.72 (95% CI 0.37–1.41), respectively. After adjusted for age, sex, body mass index, smoking status, drinking status, physical activity, depression, and OSA risk, ORs were 1.88 (95% CI 1.14–3.10) and 0.74 (95% CI 0.34–1.60), respectively. After stratifying by sex, the association of long sleep duration with metabolic syndrome was not significant (adjusted OR 0.85; 95% CI 0.27–2.71 for males, 0.67; 95% CI 0.23–1.95 for females). In males, short sleep duration was associated with an increased risk of metabolic syndrome with a crude OR of 2.93 (95% CI 1.46–5.88) and an adjusted OR of 3.41 (1.40–8.28) compared to intermediate sleep duration. In females, short sleep duration was associated with a 2.16 times higher (crude OR, 95% CI 1.29–3.62) risk of metabolic syndrome than intermediate sleep duration. However, after potential confounders (and menopausal status) were adjusted, the significance disappeared (adjusted OR; 1.44, 95% CI 0.77–2.71).

Table 2. Association between sleep duration and metabolic syndrome

Sleep duration	No. of Study population	No.(%) of metabolic syndrome	Odds ratio (95% CI)			
			Unadjusted	Model 1	Model 2	Model 3
Total (n=1,659)						
Short (≤5 hours)	152	37 (24.3)	2.07 (1.39-3.10)	2.34 (1.55-3.54)	1.95 (1.20-3.16)	1.88 (1.14-3.10)
Intermediate (5–9 hours)	1,400	188 (13.4)	1.00	1.00	1.00	1.00
Long (≥9 hours)	107	10 (9.4)	0.72 (0.37-1.41)	0.68 (0.34-1.35)	0.66 (0.31-1.39)	0.74 (0.34-1.60)
Males (n=588)						
Short (≤5 hours)	36	15 (41.7)	2.93 (1.46-5.88)	2.98 (1.47-6.02)	3.44 (1.44-8.22)	3.41 (1.40-8.28)
Intermediate (5–9 hours)	520	102 (19.6)	1.00	1.00	1.00	1.00
Long (≥9 hours)	32	5 (15.6)	0.76 (0.29-2.02)	0.75 (0.28-2.01)	0.64 (0.21-1.95)	0.85 (0.27-2.71)
Females (n=1,071)						
Short (≤5 hours)	116	22 (19.0)	2.16 (1.29-3.62)	1.86 (1.09-3.16)	1.44 (0.78-2.64)	1.44 (0.77-2.71)
Intermediate (5–9 hours)	880	86 (9.8)	1.00	1.00	1.00	1.00
Long (≥9 hours)	75	5 (6.7)	0.66 (0.26-1.68)	0.80 (0.31-2.08)	0.71 (0.25-1.99)	0.67 (0.23-1.95)

Model 1: Adjusted for age (Additionally adjusted for sex in total study population)

Model 2: Model 1 + adjusted for body mass index, smoking status, drinking status, physical activity, depression (Additionally adjusted for menopausal status in females)

Model 3: Model 2 + adjusted for obstructive sleep apnea risk

3. Association between difficulty in sleep initiation and metabolic syndrome

Table 3 displays the OR and 95% CI of difficulty in sleep initiation for metabolic syndrome before and after adjustment for the other potential confounders in study subjects. The group without difficulty in sleep initiation was used as a reference category in the logistic regression model. Overall, those who had difficulty in sleep initiation 1–4 days/week exhibited an increased risk of metabolic syndrome with a crude OR of 1.47 (95% CI 1.05–2.05) and an adjusted OR of 1.62 (95% CI 1.09–2.41) compared to the group without difficulty in sleep initiation. Even though the risk of having metabolic syndrome was higher, a significant association did not exist (crude OR 1.44; 95% CI 0.90–2.32, adjusted OR 1.59; 95% CI 0.88–2.87). In males, no values were significant. On the other hand, in females, those who had difficulty in sleep initiation 1–4 days/week revealed a 2.23 times higher (crude OR, 95% CI 1.44–3.46) risk for metabolic syndrome than those who did not have difficulty in sleep initiation. After adjusted for potential confounders, the OR was 1.75 (95% CI 1.06–2.89) and significant. In the group that had difficulty in sleep initiation 5 days or more/week, the crude OR was 2.30 (95% CI 1.28–4.13) and significant, yet in the fully adjusted model (OR 1.88; 95% CI 0.71–2.96), the significance disappeared.

Table 3. Association between difficulty in sleep initiation and metabolic syndrome

Difficulty in sleep initiation	No. of study population	No.(%) of metabolic syndrome	Odds ratio (95% CI)			
			Unadjusted	Model 1	Model 2	Model 3
Total (n=1,659)						
None	1,201	154 (12.8)	1.00	1.00	1.00	1.00
1–4days/week	321	57 (17.8)	1.47 (1.05-2.05)	1.65 (1.17-2.33)	1.64 (1.11-2.43)	1.62 (1.09-2.41)
5+days/week	137	24 (17.5)	1.44 (0.90-2.32)	1.56 (0.96-2.53)	1.86 (1.06-3.27)	1.59 (0.88-2.87)
Males (n=588)						
None	469	96 (20.5)	1.00	1.00	1.00	1.00
1–4days/week	85	19 (22.4)	1.12 (0.64-1.95)	1.12 (0.64-1.97)	1.25 (0.63-2.45)	1.32 (0.66-2.62)
5+days/week	34	7 (20.6)	1.01 (0.43-2.38)	1.00 (0.42-2.38)	2.20 (0.74-6.50)	2.20 (0.70-6.94)
Females (n=1,071)						
None	732	58 (7.9)	1.00	1.00	1.00	1.00
1–4days/week	236	38 (16.1)	2.23 (1.44-3.46)	1.95 (1.24-3.07)	1.81 (1.10-2.98)	1.75 (1.06-2.89)
5+days/week	103	17 (16.5)	2.30 (1.28-4.13)	1.86 (1.02-3.38)	1.92 (0.87-3.37)	1.88 (0.71-2.96)

Model 1: Adjusted for age (Additionally adjusted for sex in total study population)

Model 2: Model 1 + adjusted for body mass index, smoking status, drinking status, physical activity, depression (Additionally adjusted for menopausal status in females)

Model 3: Model 2 + adjusted for obstructive sleep apnea risk

4. OR (95% CI) for metabolic syndrome with sleep duration and difficulty in sleep initiation

Table 4 shows results for the association between the combined effect of sleep duration/difficulty in sleep initiation and metabolic syndrome by logistic regression analysis. The combination of sleep duration and difficulty in sleep initiation was categorized into six groups as follows: (ⅰ) short sleep duration/with difficulty in sleep initiation, (ⅱ) short sleep duration/without difficulty in sleep initiation, (ⅲ) intermediate sleep duration/with difficulty in sleep initiation, (ⅳ) intermediate sleep duration/without difficulty in sleep initiation, (ⅴ) long sleep duration/with difficulty in sleep initiation, (ⅵ) long sleep duration/without difficulty in sleep initiation. Overall, people who had difficulty in sleep initiation had a higher risk of metabolic syndrome even if the sleep duration was the same as that of a person who did not have difficulty in sleep initiation. After stratifying by sex, the results were slightly different compared to analyzing the variables separately (Table 3). According to the result for the association between difficulty in sleep initiation and metabolic syndrome, the values were not significant at all even if the OR of the fully adjusted model was higher than that of the reference group. However, when the combined effect of sleep duration and difficulty in sleep initiation was examined, the short sleep/with difficulty group revealed a 4.94 times higher (adjusted OR; 95% CI 1.05–23.21) risk of metabolic syndrome than the intermediate sleep/without difficulty group. This value was higher than the result of the short sleep/without difficulty group (adjusted OR 3.34; 95% CI 1.15–9.67). Results of other groups (intermediate sleep/with difficulty group, long sleep/with difficulty group, long sleep/without difficulty

group) were not significant. In females, the results for the association between sleep duration and metabolic syndrome were not significant after adjusted for potential confounders (Table 4). However, when the combined effect of sleep duration and difficulty in sleep initiation was examined, the crude and fully adjusted ORs of the short sleep/with difficulty group were 3.39 (95% CI 1.75–6.57) and 2.23 (95% CI 1.01–4.94), respectively. The intermediate sleep/with difficulty group had a higher risk of metabolic syndrome than the intermediate sleep/without difficulty group (crude OR 2.34; 95% CI 1.49–3.68, adjusted OR 1.84; 95% CI 1.09–3.09). The results of the short sleep/without difficulty and long sleep/without or with difficulty groups were not significant at all.

Table 4. Odds ratio (95% CI) for metabolic syndrome with sleep duration and difficulty in sleep initiation

Group	No. of Study population	No.(%) of metabolic syndrome	Odds ratio (95% CI)			
			Unadjusted	Model 1	Model 2	Model 3
Total (n=1,659)						
Short sleep / Difficulty (+)	76	18 (23.7)	2.24 (1.28-3.92)	2.78 (1.55-4.97)	2.58 (1.32-5.02)	2.50 (1.27-4.94)
Short sleep / Difficulty (-)	76	19 (25.0)	2.40 (1.39-4.17)	2.69 (1.53-4.73)	2.12 (1.06-4.22)	2.07 (1.03-4.15)
Intermediate sleep / Difficulty (+)	357	61 (17.1)	1.49 (1.07-2.07)	1.66 (1.18-2.34)	1.78 (1.20-2.64)	1.80 (1.21-2.68)
Intermediate sleep / Difficulty (-)	1,043	127 (12.2)	1.00	1.00	1.00	1.00
Long sleep / Difficulty (+)	25	2 (8.0)	0.63 (0.15-2.69)	0.66 (0.15-2.91)	0.52 (0.11-2.50)	0.60 (0.42-2.43)
Long sleep / Difficulty (-)	82	8 (9.8)	0.78 (0.37-1.66)	0.82 (0.38-1.78)	0.89 (0.38-2.08)	1.01 (0.42-2.43)
Males (n=588)						
Short sleep / Difficulty (+)	10	4 (40.0)	2.77 (0.77-10.06)	2.88 (0.79-10.50)	3.99 (0.88-18.03)	4.94 (1.05-23.21)
Short sleep / Difficulty (-)	26	11 (42.3)	3.05 (1.35-6.89)	3.09 (1.35-7.04)	3.62 (1.26-10.35)	3.34 (1.15-9.67)
Intermediate sleep / Difficulty (+)	102	21 (20.6)	1.08 (0.63-1.85)	1.08 (0.63-1.85)	1.42 (0.73-2.75)	1.49 (0.76-2.91)
Intermediate sleep / Difficulty (-)	418	81 (19.4)	1.00	1.00	1.00	1.00
Long sleep / Difficulty (+)	7	1 (14.3)	0.69 (0.08-5.84)	0.70 (0.08-5.92)	0.81 (0.08-8.59)	1.15 (0.11-12.44)
Long sleep / Difficulty (-)	25	4 (16.0)	0.79 (0.27-2.37)	0.78 (0.26-2.34)	0.65 (0.19-2.27)	0.88 (0.24-3.18)
Females (n=1,071)						
Short sleep / Difficulty (+)	66	14 (21.2)	3.39 (1.75-6.57)	2.70 (1.37-5.32)	2.32 (1.08-5.00)	2.23 (1.01-4.94)
Short sleep / Difficulty (-)	50	8 (16.0)	2.40 (1.06-5.41)	2.06 (0.89-4.73)	1.31 (0.48-3.57)	1.36 (0.50-3.72)
Intermediate sleep / Difficulty (+)	255	40 (15.7)	2.34 (1.49-3.68)	2.02 (1.27-3.20)	1.90 (1.14-3.17)	1.84 (1.09-3.09)
Intermediate sleep / Difficulty (-)	625	46 (7.4)	1.00	1.00	1.00	1.00
Long sleep / Difficulty (+)	18	1 (5.6)	0.74 (0.10-5.69)	0.71 (0.09-5.54)	0.39 (0.20-2.48)	0.36 (0.04-3.23)
Long sleep / Difficulty (-)	57	4 (7.0)	0.95 (0.33-2.74)	1.18 (0.40-3.49)	1.32 (0.40-4.30)	1.27 (0.38-4.24)

Model 1: Adjusted for age (Additionally adjusted for sex in total study population)

Model 2: Model 1 + adjusted for body mass index, smoking status, drinking status, physical activity, depression (Additionally adjusted for menopausal status in females)

Model 3: Model 2 + adjusted for obstructive sleep apnea risk

5. Association between OSA and metabolic syndrome components

In the case of OSA risk, those who had a history of diagnosed hypertension were included in Category 3 of the Berlin Questionnaire and had the “high blood pressure” component of metabolic syndrome, so we examined the association with each component of metabolic syndrome rather than with the metabolic syndrome prevalence of the subjects (Table 5). In all metabolic syndrome components, the high risk of OSA group revealed a higher risk of each metabolic syndrome component than the low risk of OSA group. However, after adjusting potential confounders including other metabolic syndrome components, the significance disappeared in the elevated triglyceride and elevated fasting glucose components. In the case of the low HDL-cholesterol component, only in females, the high risk of OSA group exhibited a 1.49 times higher (95% CI 1.03–2.16) risk than the low risk of OSA group. Compared to the low risk of OSA group, the high-risk group had a 3.61 times higher (95% CI 2.76–4.71) risk of abdominal obesity after adjusting the multiple potential confounders. Even when males and females were viewed separately, the results were similar. The adjusted OR was 3.99 (95% CI 2.66–5.99) in males and 3.54 (95% CI 2.45–5.10) in females, and all results were statistically significant. Moreover, the high risk of OSA group revealed a 2.39 times higher (adjusted OR; 95% CI 1.82–3.14) risk for the high blood pressure component in overall participants, 1.53 times higher (adjusted OR; 95% CI 1.01–2.31) risk in male participants, and 3.36 times higher (adjusted OR; 95% CI 2.32–4.87) risk in female participants.

Table 5. Association between obstructive sleep apnea and metabolic syndrome components

A) Abdominal obesity

Obstructive sleep apnea risk	Odds ratio (95% CI)	
	Unadjusted	Adjusted for age, sex, smoking status, drinking status, physical activity, depression, sleep duration, triglyceride, HDL-cholesterol, fasting glucose level
Total (n=1,659)		
Low risk	1.00	1.00
High risk	4.65 (3.63-5.95)	3.61 (2.76-4.71)
Males (n=588)		
Low risk	1.00	1.00
High risk	4.47 (3.07-6.52)	3.99 (2.66-5.99)
Females (n=1,071)		
Low risk	1.00	1.00
High risk	4.37 (3.12-6.12)	3.54 (2.45-5.10)

B) Triglyceride≥150mg/dL

Obstructive sleep apnea risk	Odds ratio (95% CI)	
	Unadjusted	Adjusted for age, sex, smoking status, drinking status, physical activity, depression, sleep duration, waist circumference, HDL-cholesterol, fasting glucose level
Total (n=1,659)		
Low risk	1.00	1.00
High risk	2.75 (2.15-3.52)	1.30 (0.96-1.75)
Males (n=588)		
Low risk	1.00	1.00
High risk	2.30 (1.62-3.27)	1.32 (0.86-2.02)
Females (n=1,071)		
Low risk	1.00	1.00
High risk	2.36 (1.63-3.41)	1.26 (0.81-1.96)

C) Low HDL-cholesterol

Obstructive sleep apnea risk	Odds ratio (95% CI)	
	Unadjusted	Adjusted for age, sex, smoking status, drinking status, physical activity, depression, sleep duration, waist circumference, triglyceride, fasting glucose level
Total (n=1,659)		
Low risk	1.00	1.00
High risk	1.87 (1.46-2.38)	1.33 (0.99-1.78)
Males (n=588)		
Low risk	1.00	1.00
High risk	1.87 (1.24-2.84)	1.09 (0.65-1.83)
Females (n=1,071)		
Low risk	1.00	1.00
High risk	2.35 (1.71-3.23)	1.49 (1.03-2.16)

Table 5. Association between obstructive sleep apnea and metabolic syndrome components (continued)

D) Blood pressure ≥ 130/85 mmHg or use of anti-hypertensive medication

Obstructive sleep apnea risk	Odds ratio (95% CI)	
	Unadjusted	Adjusted for age, sex, smoking status, drinking status, physical activity, depression, sleep duration, waist circumference, triglyceride, HDL-cholesterol, fasting glucose level
Total (n=1,659)		
Low risk	1.00	1.00
High risk	3.29 (2.60-4.15)	2.39 (1.82-3.14)
Males (n=588)		
Low risk	1.00	1.00
High risk	2.11 (1.49-2.97)	1.53 (1.01-2.31)
Females (n=1,071)		
Low risk	1.00	1.00
High risk	3.98 (2.88-5.50)	3.36 (2.32-4.87)

E) Fasting glucose ≥ 100 mg/dL or history of diabetes diagnosis or use of anti-diabetes medication

Obstructive sleep apnea risk	Odds ratio (95% CI)	
	Unadjusted	Adjusted for age, sex, smoking status, drinking status, physical activity, depression, sleep duration, waist circumference, triglyceride, HDL-cholesterol level
Total (n=1,659)		
Low risk	1.00	1.00
High risk	2.25 (1.70-2.93)	1.24 (0.90-1.72)
Males (n=588)		
Low risk	1.00	1.00
High risk	2.14 (1.44-3.20)	1.49 (0.94-2.35)
Females (n=1,071)		
Low risk	1.00	1.00
High risk	1.82 (1.18-2.80)	1.00 (0.62-1.62)

IV. DISCUSSION

In previous studies, assessment of sleep duration has been mainly used to evaluate the status of sleep. However, measuring sleep duration only is insufficient for understanding global sleep status, which consists of not only sleep duration but also sleep quality and sleep disorders. These sleep-related factors include quantitative and qualitative variables, which has made sleep status difficult to understand. Considering both aspects, we evaluated sleep duration (quantitative variable) and difficulty in sleep initiation and OSA risk (qualitative variables). To evaluate these two aspects of sleep parameters, we used self-reported questionnaire. For the 1,659 participating Korean adults aged 30 to 64 years, we examined the associations of metabolic syndrome with sleep duration and difficulty in sleep initiation separately and the combined effect of the two variables. We also examined the relationship between OSA risk and each of the metabolic syndrome components. When sleep duration and difficulty in sleep initiation were examined separately, our results showed a significant association of metabolic syndrome with short sleep duration, particularly in male participants, and with difficulty in sleep initiation in female participants. However, when the combined effect of sleep duration and difficulty in sleep initiation was examined in males and females, it revealed that it is associated with metabolic syndrome.

So far, few studies have reported on the association between metabolic syndrome and global sleep status, especially in Korea. Thus, the current study provides good evidence of the relationship between sleep parameters and metabolic syndrome. As far as we know, there are no studies on the association between the combined effect of sleep duration/difficulty in sleep initiation and metabolic syndrome, so our results are

meaningful, as they consider the relationship between quantitative and qualitative aspects of sleep parameters together and metabolic syndrome.

Previous studies have produced diverse results on the association between sleep parameters and metabolic syndrome, possibly due to the diversity in the characteristics of the study subjects or the considered variables, including sleep-related parameters.

Many previous studies have reported that short and long sleep durations related with metabolic syndrome generally present a U-shaped curvilinear pattern (Hall et al., 2008; Stefani et al., 2013). In the present study, concerning only sleep duration, the short sleep duration (≤ 5 hours) showed a higher prevalence of metabolic syndrome, particularly in male participants. In our study, long sleep duration seems to be shown rather negative association with metabolic syndrome, even if the value was not significant at all. Our study population was relatively healthy adults without history of cardiovascular and cerebrovascular diseases. Moreover, concerning the age of study subjects, our study subjects were middle-aged (mean age was 49.1 years), and 93% of male subjects were currently working. In addition, only 6.5% of the total subjects reported a long sleep duration. Considering that, sleep duration may be influenced by age and working status, and this difference between the studies could explain the different results. Therefore, the present study was focused on middle-aged Koreans who mainly contribute to productivity. Thus, we need to expand the age of participants to clarify the relationship between long sleep duration and metabolic syndrome.

Concerning difficulty in sleep initiation, the prevalence of metabolic syndrome was presently higher in the group that had difficulty in sleep initiation than in the group that did not have difficulty (Table 3). According to previous studies, as sleep quality decreases, metabolic syndrome becomes more common, with elevated insulin resistance resulting from central adiposity being involved in this relationship (Hung et al., 2013;

Jennings et al., 2007; Lee et al., 2013; Sasanabe et al., 2006). In previous studies, aspects of sleep quality have been assessed by diverse way. Many studies have been assessed sleep status by Pittsburgh Sleep Quality Index (PSQI) which is reliable and valid questionnaire for evaluating the aspects of sleep quality in Korea (Sohn et al., 2012). However, our analysis did not use PSQI to evaluate sleep quality, because we used different form of questionnaire from the PSQI. Consequently, compared to previous studies, the meaning of sleep quality was different, so we examined the difficulty in sleep initiation by self-reported data. This study indicated that those who had difficulty in sleep initiation had a higher metabolic syndrome risk, especially females, even if they slept long enough. However, concerning the combined effect of sleep duration and difficulty in sleep initiation, our study suggested that considering sleep duration and difficulty together is necessary when evaluating the association with metabolic syndrome risk. Females who had difficulty in sleep initiation and a short sleep duration had a higher risk of metabolic syndrome. A similar pattern was observed in male participants, as people who had difficulty in sleep initiation had a higher risk of metabolic syndrome, even if they belonged to the same sleep duration group.

Concerning the OSA risk, the high-risk group showed a higher prevalence of metabolic syndrome components of abdominal obesity and high blood pressure compared to the other groups (Table 5). Sasanabe et al. (2006) reported that both males and females with OSA (Apneal-Hypopnea Index [AHI] ≥/hour) had higher ORs for metabolic syndrome compared with controls (OR 3.47 and 6.59; 95% CI 1.84–6.53 and 1.47–29.38, respectively). After the adjustment for age and body mass index, the adjusted OR of the AHI ≥ 15 /hour group was 2.08 (1.41–3.06) in males and 2.24 (0.84–5.99) in females. Lee et al. (2013) reported results similar to ours in their study, which examined the relationship between OSA risk and metabolic syndrome in 301 Koreans. The results of

their study showed a higher prevalence of the abdominal obesity component and a number of metabolic syndrome components in the high risk of OSA group than the low risk of OSA group. According to previous studies, OSA seems to affect the pathway of metabolites in various ways. However, considering the indicators for determining the risk of OSA according to the Berlin Questionnaire, including body mass index and hypertension, caution is needed in the interpretation of the relationship between OSA and metabolic syndrome.

The mechanism of the relationship between sleep disorders and metabolic syndrome has not been clarified due to a lack of confirming evidence. Sleep rhythm is regulated by the hypothalamus. Sleep disorders activate the hypothalamic-pituitary-adrenal axis (HPA), enhancing the secretion of stress hormones, such as cortisol and catecholamine. These excess secretions finally lead to an increased risk of metabolic syndrome. The sympathomimetic state induced by poor sleep quality reduces leptin levels and elevates ghrelin levels, which is also related with obesity. Furthermore, it enhances stress hormone secretion (Rangaraj &Knutson, 2015).

Our study has some advantages. We were able to consider the comprehensive relationships taking lifestyles and depression into account. Moreover, we were able to evaluate not only sleep duration but also the comprehensive sleep status, including difficulty in sleep initiation and risk of OSA. In addition, this is the first study evaluating the combined effect of sleep duration and difficulty in sleep initiation on metabolic syndrome. However, our study has some limitations. First, this study was designed as a cross-sectional analysis. Thus, the causal relationship between sleep parameters and metabolic syndrome could not be investigated. Second, our study population was not representative of the entire middle-aged Korean population. The subjects could be slightly different from the general population, as only participants in the CMERC study

were included in this study. The prevalence of metabolic syndrome was lower in this study (14.1%) than in the KNHANES-Ⅵ (2013) (26.4%) which is nationally representative survey of the non-institutionalized civilian population, and is annually carried out by the Korea Centers for Disease Control and Prevention (KCDC). Although directly comparing the result of the KNHANES-Ⅵ (2013) is inappropriate because of differences in the age structure and sex ratio, our study population seems to be relatively healthier than the general population. Third, we evaluated sleep parameters using self-report questionnaires, which may be inaccurate because of the possibility of the answers differing from the truth. Although the accelerometer is used as an objective index for evaluating the current sleep state, it also has a limitation. It is not reflecting average physical activity level as it only measures 7 days. Combining the accelerometer and self-report questionnaires may have led to a different result.

V. CONCLUSION

Our cross-sectional study using data from the CMERC study 2013 and 2014 suggested that sleep parameters including sleep duration, difficulty in sleep initiation, and OSA risk were associated with metabolic syndrome among healthy middle-aged Koreans.

In male participants, short sleep duration (≤ 5 hours/day) was associated with an increased risk of metabolic syndrome. On the other hand, females who had difficulty in sleep initiation were at a higher risk of metabolic syndrome. However, when the relationship between the combined effect of sleep duration/difficulty in sleep initiation and metabolic syndrome was examined, the results showed that short sleep duration and difficulty in sleep initiation were both related to metabolic syndrome in both male and female participants. This may imply that quantitative and qualitative aspects of sleep should be considered together when evaluating sleep status. Moreover, when we examined the relationship of OSA risk and metabolic syndrome components, the high risk of OSA group was found to be associated with abdominal obesity by measuring waist circumference and blood pressure. However, considering the indicators for determining the risk of OSA, including body mass index and diagnosed hypertension, caution is needed in the interpretation.

Further studies are warranted to generalize our results. If future studies establish the causality between sleep and metabolic syndrome, and affirm that various sleep parameters are risk factors for metabolic syndrome, appropriate sleep management may help prevent metabolic syndrome development.

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Korean Abstract

건강한 한국 중년 인구에서 수면과 대사증후군과의 관련성

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김나래

연구 배경 및 목적: 수면 상태는 여러 건강 문제와도 밀접한 연관성이 있다고 보고되어 왔다.여러 선행연구들을 통해 수면 상태와 대사증후군과의 관련성이 연구되어왔지만, 수면 시간이나 수면의 질, 그리고 동반되는 수면 장애들까지 복합적으로 고려한 연구들은 아직 부족한 상태이다. 이에, 본 연구에서는 건강한 한국 중년 인구를 대상으로 수면 시간, 수면유도장애 그리고 수면무호흡증과 대사증후군과의 독립적인 관련성을 연구하고자 한다.

연구 방법: 본 연구는 지역사회기반 전향적 코호트인 Cardiovascular and Metabolic diseases Etiology Research Center (CMERC) study의 일부로, 2013년과 2014년에 연구 참여에 동의하고 기반조사를 마친 30세에서

64세의 성인을 대상으로 시행되었다.

수면 시간과 수면유도장애의 경험 여부 그리고 수면무호흡증의 위험과 대사증후군과의 독립적인 관련성을 보기 위해 단순회귀분석과 다중회귀분석을 시행하였으며, 혼란변수로는 성, 연령, 체질량지수, 흡연상태, 음주상태, 신체활동량, 우울증 여부 등을 보정하였다.

연구 결과: 수면 시간과 수면유도장애 경험 여부를 각각 대사증후군과의 관련성을 보았을 때, 남자에서는 짧은 수면시간이 대사증후군과 통계적으로 유의한 관련성이 있었지만 (Odds Ratio (OR) 3.41; 95% CI 1.40-8.28) 여자에서는 통계적으로 유의한 관련성을 보이지 않았다. 여자에서는 주 1-4일 수면유도장애를 겪는 군이 대사증후군과 독립적인 관련성이 있었고 (OR 1.75; 95% CI 1.06-2.89), 남자에서는 통계적으로 유의한 관련성을 보이지 않았다. 수면시간과 수면유도장애의 경험 여부를 결합하여 그 결과를 보았을 때, 남자와 여자에서 모두 수면 시간이 짧으면서 수면 유도 장애를 겪고 있는 군에서 대사증후군일 오즈비가 높게 나타났다 (각각 OR 4.94; 95% CI 1.05-23.21, OR 2.23; 95% CI 1.01-4.94). 그리고 수면무호흡증과 대사증후군 각각의 지표들과의 관련성을 보았을 때, 남자와 여자 모두에서 수면무호흡증 고위험군은 복부 비만 지표 (각각 OR 3.99; 95% CI 2.66-5.99, OR 3.54 95% CI 2.45-5.10)와 고혈압 지표 (각각 OR 1.53; 95% CI 1.01-2.31, OR 3.36; 95% CI 2.43-4.87)에서 독립적인 관련성이 있었으며, 고밀도지질단백질 콜레스테롤의 경우 여자에서만 통계적으로 유의한 관련성을 보였다 (OR 1.49;

95% CI 1.03-2.16)

결론: 본 연구에서는 지역사회 거주 한국 중년 인구에서는 짧은 수면시간과 수면 유도 장애의 경험이 모두 대사증후군과 양의 관련성을 보였다. 이는 수면의 양적인 측면과 질적인 측면을 함께 고려하는 것이 필요하다는 것을 시사한다. 또한 남자와 여자 모두에서 수면무호흡증의 고위험군에 속하는 사람들이 복부 비만이나 높은 혈압의 지표와 독립적인 관련성이 있었지만, 수면무호흡증의 위험도를 선별하는 지표에 체질량지수와 고혈압 진단여부가 포함되어 있다는 것을 고려하여볼 때, 해석에 주의가 필요할 것으로 사료된다.

핵심어: 수면, 대사증후군, 한국, 중년