

Associations of sleep duration with open angle glaucoma in the Korea national health and nutrition examination survey

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Abstract

The aim of this study is to investigate the relationship between sleep duration and glaucoma, stratified by obesity status.

This study was conducted using data from the Korean National Health and Nutrition Examination Survey V 2010 to 2012. Open-angle glaucoma was diagnosed according to the International Society of Geographical and Epidemiological Ophthalmology criteria. Subjects were divided into subgroups based on those who were overweight (body mass index ≥ 25 kg/m² or < 25 kg/m²) or with abdominal obesity (based on waist circumference). Multiple logistic regression analysis was done to estimate the magnitude of the association between sleep duration (< 7 h, 7 – < 9 , or ≥ 9 hours) and prevalence of glaucoma in the total population and in the subgroups.

Individuals who slept < 5 hours per night had the highest prevalence of glaucoma ($5.55 \pm 1.09\%$), followed by those who slept ≥ 9 hours per night ($4.56 \pm 0.10\%$), and then by those who slept 5 to < 6 hours per night ($4.15 \pm 0.68\%$), which revealed a U-shaped pattern (P for trend = 0.072). Among overweight individuals, subjects who slept < 7 hours and those who slept ≥ 9 hours were significantly more likely to have glaucoma compared with subjects who slept 7 to < 9 hours after adjusting for survey year, age, sex, smoking, drinking, exercise, education level, household income, hypertension, intraocular pressure, stress, and depression (odds ratio, 2.41; 95% confidence interval, 1.14–5.03). Unlike for overweight individuals, sleep duration in nonoverweight individuals was not statistically significantly associated with glaucoma.

Our results reveal a U-shaped association between sleep duration and the prevalence of glaucoma. An effect of sleep duration on glaucoma was present in the subgroup of overweight patients.

Abbreviations: BMI = body mass index, BP = blood pressure, FDT = frequency-doubling technology, FPG = fasting plasma glucose, HCDR = horizontal cup-to-disc ratio, HDL-C = high-density lipoprotein-cholesterol, HTN = hypertension, IOP = intraocular pressure, ipRGC = intrinsically photosensitive retinal ganglion cell, KNHANES = Korean National Health and Nutrition Examination Survey, MetS = metabolic syndrome, OAG = open-angle glaucoma, SCN = suprachiasmatic nucleus, SE = standard errors, TG = triglyceride, VCDR = vertical cup-to-disc ratio, WC = waist circumference.

Keywords: body mass index, glaucoma, obesity, open-angle, sleep, waist circumference

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1. Introduction

Glaucoma is an optic neuropathy characterized by progressive loss of retinal ganglion cells and their axons, which leads to structural and functional damage to the optic nerve. Corresponding visual field deterioration occurs in the area of the optic nerve head and the retinal nerve fiber layer if the disease is not controlled. Glaucoma is a multifactorial disease, and its precise pathogenesis remains unclear. Intraocular pressure (IOP) is the most important risk factor for the development and progression of glaucoma. However, reducing IOP does not guarantee a halt in disease progression.^[1–5] Some patients show glaucoma progression despite a reduction in IOP.^[5]

Besides IOP, blood flow abnormalities, immunoregulatory mechanisms, and the susceptibility of ganglion cells to apoptosis have been put forth as factors in the pathogenesis of glaucoma. Recently, sleep disturbances, characterized by dysregulation of circadian rhythms, were found to be associated with glaucoma.^[6] In addition, glaucoma patients have high incidences of sleep disorders,^[7,8] depression, and anxiety.^[9,10]

Regarding the association between sleep disturbance and glaucoma, glaucoma may lead to circadian disruption through affection of the retinothalamic tract^[11] and thus, to sleep

disorders. In addition, melatonin, the major coordinator of sleep and wake cycles,^[12] has been implicated in the pathogenesis of glaucoma. Melatonin protects retinal neurons against oxidative stress, as it acts as a scavenger of light-induced free radicals.^[13] In an animal model, topical administration of melatonin lowered IOP in a dose-dependent manner.^[13] Orally administered melatonin also significantly decreased IOP in humans,^[14] although the intraocular role of melatonin may be directly related to the central actions of the hormone.^[15–17]

Furthermore, melatonin mediates the link between the external environment and the internal, circadian rhythm-driven physiological and behavioral processes necessary for a healthy metabolism and for the optimization of energy balance and body weight regulation.^[18] Melatonin is responsible for the maintenance of energy balance mainly by regulating energy flow to and from energy stores and directly regulating energy expenditure through the activation of brown adipose tissue.^[19] Thus, the association between sleep disturbances and glaucoma may be affected by body phenotype. Despite the possible clinical significance of this issue, the association between glaucoma and sleep disturbances according to obesity status has not been addressed in a large population-based study. The aim of the current study was to investigate the relationship between sleep duration and glaucoma, stratified by obesity status.

2. Subjects, materials, and methods

2.1. Study population

This study was conducted using data from the Korean National Health and Nutrition Examination Survey V (KNHANES) 2010 to 2012. KNHANES is a cross-sectional, nationally representative sample of the Korean noninstitutionalized civilian population aged 1 year and above; it employs a rolling sampling design that allows for complex, stratified, multistage probability analysis. KNHANES is maintained by the Korean Ministry of Health and Welfare to continuously monitor the health and nutritional status of people living in South Korea.^[20] Individuals aged 40 years and older who completed ophthalmologic surveys were included in the current study. A total of 25,534 subjects participated in surveys administered from 2010 to 2012; among them, a total of 19,599 subjects completed ophthalmologic surveys. Of those 19,599 subjects, 12,881 (65.7%) were over 40 years of age. After excluding 3471 cases with missing data, a total of 9410 subjects were finally included in the study population. The KNHANES V was conducted according to the guidelines set forth in the Declaration of Helsinki, and was carried out by specially trained interviewers who were not provided with any prior information about the participants. All participants signed an informed consent form. The present study was approved by the Institutional Review Board of the Catholic University of Korea.

2.2. Measurements

In the health interview, trained interviewers recorded information about participant demographics and health-related characteristics, including age, education level, area of residence, and household income. Information about lifestyle characteristics, including smoking, drinking alcohol, exercise, sleep duration, stress, and depression, was recorded from self-reported questionnaires. Subjects were classified into a high-education group if they had completed high school or university. Area of residence

was categorized as urban (8 major cities in South Korea: Seoul, Gyeonggi, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) or rural (8 other provinces in South Korea). Income was divided into quartiles after adjusting for the number of individuals living in a household. Participants were grouped into the low-income group if their household income fell in the lowest quartile. Smoking status was recorded as either nonsmoking or smoking. A smoker was defined as having smoked more than 100 cigarettes in his/her lifetime, whereas a nonsmoker was defined as having smoked fewer than 100 cigarettes. Alcohol consumption was also classified into 2 groups: non-to-moderate drinkers (<30.0 g alcohol/d) and heavy drinkers (≥ 30.0 g alcohol/d). Regular exercise was defined as moderate-intensity physical activity (e.g., carrying light loads, cycling at a regular pace, playing tennis, etc.) for at least 20 minutes at a time at least 3 times a week. Sleep duration was assessed based on the response to the question, "What was your average daily sleep duration during the past year at night?" We divided the participants according to sleep duration: <5, 5 to <6, 6 to <7, 7 to <8, 8 to <9, and ≥ 9 hours. Stress level was defined as having experienced very much or only a little stress in the past year. Depressive symptoms were assessed with the following yes-or-no question: "In the past year, have you felt extremely sorrowful or despairing for more than 2 weeks?"

Height was measured to the nearest 0.1 cm using a portable stadiometer (SECA 225, SECA Deutschland, Hamburg, Germany) with the participants standing barefoot. Weight was measured to the nearest 0.1 kg using an electronic scale (GL-6000-20, CAS KOREA, Seoul, Korea) while the participants wore a lightweight gown. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Waist circumference (WC) was measured after normal expiration to the nearest 0.1 cm using a measuring tape (SECA 200, SECA Deutschland) at the midpoint between the lower margin of the ribcage and the iliac crest at the mid-axillary line. Blood pressure (BP) was measured from the right arm using a standard mercury sphygmomanometer (Baumanometer, WA Baum Co, New York) after 5 minutes of rest in a sitting position. Systolic and diastolic BP were measured 3 times at 30-second intervals, and the average of the last 2 values was used for analysis. Hypertension (HTN) was identified in those participants with a systolic BP ≥ 140 mm Hg, a diastolic BP ≥ 90 mm Hg, or who were taking antihypertensive medications.

Venous blood samples were taken after participants fasted for at least 8 hours. Fasting plasma glucose (FPG), high-density lipoprotein-cholesterol (HDL-C), total cholesterol, and triglyceride (TG) levels were measured using a Hitachi Automatic Analyzer 7600 (Hitachi, Tokyo, Japan). Low-density lipoprotein cholesterol was calculated using the Friedewald formula. Diabetes mellitus was defined as FPG ≥ 126 mg/dL, or when patients were taking insulin or antihyperglycemic medications.

All ophthalmologic examinations were performed by ophthalmologists using a slit-lamp (Haag-Streit model BQ-900; Haag-Streit AG, Koeniz, Switzerland). Participants underwent ophthalmologic interviews, visual acuity measurements, autorefractometry, slit-lamp examinations of the anterior segment, and IOP measurements. Refraction measurements were performed using an autorefractor-keratometer (KR 8800; Topcon, Tokyo, Japan) and were converted into spherical equivalents and calculated as the spherical value plus half the astigmatic value. IOP was measured once per eye with a Goldmann applanation tonometer during slit-lamp examination. A digital nonmydriatic retinal camera and a Nikon D-80 digital camera (Nikon Inc,

Tokyo, Japan) were used to obtain fundus images from all participants, without dilating the pupils. A visual field test that employed frequency-doubling technology (FDT) (Humphrey Matrix; Carl Zeiss Meditec Inc, Dublin, CA) using the N-30-1 screening test was performed if the participants were suspected of having glaucoma and met any of the following criteria: IOP ≥ 22 mm Hg or presence of a glaucomatous optic disc; presence of a vertical cup-to-disc ratio (VCDR) or horizontal cup-to-disc ratio (HCDR) ≥ 0.5 ; presence of an optic disc hemorrhage; presence of a retinal nerve fiber layer defect; and nonadherence to the ISNT rule (i.e., normally, the neuroretinal rim thicknesses are in the following order: inferior > superior > nasal > temporal). FDT was repeated if the rate of fixation errors was >0.33 or if the false-positive rate was >0.33 . Only 1 eye from each subject was used for statistical analysis. The data from eyes diagnosed with open-angle glaucoma (OAG) were used for analysis, and the worse eye was chosen for analysis in cases of bilateral glaucoma. For control subjects, the right eye was chosen for analysis because IOPs in the right and left eyes are highly correlated with one another^[21] (Pearson correlation coefficient = 0.86, $P < 0.001$).

2.3. Definition of diseases

Glaucoma was taken to be synonymous with OAG in this study. OAG was diagnosed based on the International Society of Geographical and Epidemiological Ophthalmology criteria. OAG entails the presence of an open angle (peripheral anterior chamber depth $>1/4$ corneal thickness) as well as any one of the following category 1 or 2 criteria: category 1, both a visual field defect consistent with glaucoma and either a VCDR ≥ 0.7 (97.5th percentile) or a difference in VCDR of ≥ 0.2 between the eyes (97.5th percentile) (if FDT results were available and had a fixation error and false-positive error ≤ 1); category 2, a VCDR ≥ 0.9 (99.5th percentile) or a difference in VCDR of ≥ 0.3 between the eyes (99.5th percentile) (if FDT results were absent, or if FDT results had a fixation error and false-positive error ≥ 2). IOP was not taken into consideration when establishing a diagnosis of OAG.

In this study, subjects with a BMI ≥ 25 kg/m² were defined as being overweight. Metabolic syndrome (MetS) was diagnosed according to the modified definition put forth by the National Cholesterol Education Program Adult Treatment Panel III. The WC criteria were modified for the Asian population. MetS was diagnosed when more than 3 of the following factors were present: WC ≥ 90 cm for men or ≥ 80 cm for women; serum TGs ≥ 150 mg/dL, or medical treatment for high TGs; HDL-C < 40 mg/dL for men or < 50 mg/dL for women, or treatment for HDL-C abnormalities; systolic BP ≥ 130 mm Hg or diastolic BP ≥ 85 mm Hg, or being on antihypertensive medication; FPG ≥ 100 mg/dL, or being on antihyperglycemic medication.

2.4. Statistical analysis

Statistical analyses were done using SAS (version 9.3; SAS Institute Inc, Cary, NC). The KNHANES sampling weights were used to acquire nationally representative prevalence estimates. All analyses were adjusted for survey year to minimize variation between years. Data are presented as means \pm standard errors (SE) for continuous variables or proportions for categorical variables. The general and clinical characteristics of the subjects were compared according to the presence of glaucoma. Patients were assigned to the overweight subgroup if their BMI was ≥ 25 kg/m² or if they had abdominal obesity (based on waist circumference). In each subgroup, the prevalence of glaucoma

was determined given sleep duration. Multiple logistic regression analysis was done to estimate the magnitude of the association between sleep duration (<7 , 7 – <9 , or ≥ 9 hours) and the prevalence of glaucoma in the total population and in each subgroup after adjusting for survey year, age, and sex in Model 2. Model 3 was additionally adjusted for smoking, drinking, exercise, education level, and household income. Model 4 was further adjusted for HTN, IOP, stress, and depression. A P value < 0.05 was considered statistically significant.

3. Results

The overall prevalence of OAG was 3.91%. A comparison of the clinical and biochemical parameters of subjects with glaucoma and without glaucoma is presented in Table 1. Age, systolic BP, IOP, refractive error, education level, area of residence, household income, regular physical activity, and diagnoses of HTN and MetS were significantly different between subjects with glaucoma and those without glaucoma (all $P < 0.05$).

The prevalence of glaucoma according to sleep duration is shown in Fig. 1. Individuals who slept less than 5 hours per night had the highest prevalence of glaucoma ($5.55 \pm 1.09\%$), which was followed by those who slept ≥ 9 hours ($4.56 \pm 0.10\%$), and then by those who slept 5 to <6 hours ($4.15 \pm 0.68\%$), showing a U shaped pattern (P for trend = 0.072).

Figure 2 shows the prevalence of glaucoma according to sleep duration in the subgroups of patients who were overweight or who had abdominal obesity. In the overweight subgroup, the prevalence of glaucoma was highest in subjects who slept less than 5 hours per night, followed by those who slept 9 hours or more, showing a U-shaped pattern (P for trend = 0.056), whereas no trend was observed in nonoverweight subjects ($P = 0.274$). In the patient subgroup with abdominal obesity, the prevalence of glaucoma was highest in subjects who slept 9 hours or more, followed by those who slept less than 5 hours, showing a similar U-shaped pattern (P for trend = 0.022). In contrast, there was no trend in the patient subgroup without abdominal obesity ($P = 0.499$).

Table 2 shows the results of multiple logistic regression analyses on the prevalence of glaucoma according to sleep duration in the total population and the subgroups. Among overweight individuals, subjects who slept <7 hours and those who slept ≥ 9 hours were significantly more likely to have glaucoma compared with subjects who slept 7 to <9 hours after adjusting for survey year, age, and sex (Model 2; OR, 2.15; 95% CI, 1.04–4.43), which remained significant after additional adjustment for smoking, drinking, exercise, education level, household income, HTN, IOP, stress, and depression (Model 4; OR, 2.41; 95% CI, 1.14–5.03) (P for trend = 0.036). Unlike the case for overweight individuals, sleep duration in nonoverweight individuals was not significantly associated with glaucoma (P for trend = 0.849). In individuals with abdominal obesity, subjects who slept ≥ 9 hours were significantly more likely to have glaucoma compared with those who slept 7 to <9 hours after adjusting for survey year, age, and sex (Model 2; OR, 2.56; 95% CI, 1.27, 5.14), and the results remained significant after additional adjustment for confounding factors (Model 4; OR, 2.15; 95% CI, 1.07–4.31) (P for trend = 0.094).

4. Discussion

In this study, we found that the prevalence of glaucoma was greater in subjects with short sleep duration and those with long

Table 1**Characteristics of the study population.**

	Glaucoma		P value
	No	Yes	
Number	9042	368	
Age, y	54.7±0.2	60.8±0.9	<0.001
BMI, kg/m ²	24.11±0.04	23.73±0.23	0.113
Waist circumference, cm	82.8±0.2	82.9±0.7	0.865
Systolic BP, mm Hg	122.3±0.3	128.4±1.3	<0.001
Diastolic BP, mm Hg	78.2±0.2	78.4±0.7	0.797
IOP, mm Hg	14.6±0.1	15.4±0.3	<0.001
Refractive error (diopter)	-0.26±0.04	-0.83±0.24	0.018
Sleep duration, h	6.69±0.02	6.71±0.13	0.859
Stress, %	24.3 (0.6)	23 (3.0)	0.692
Depression, %	13.9 (0.4)	16.6 (2.6)	0.275
Current smoker, %	20.2 (0.6)	22 (3.1)	0.551
Current drinker (heavy, %)	9.6 (0.4)	6.9 (1.9)	0.235
Education level (≥9 y, %)	56.4 (0.9)	38.6 (3.6)	<0.001
Area of residence (urban, %)	77.2 (1.9)	70.8 (3.9)	0.031
Low income (lowest quartile, %)	18.8 (0.7)	32.7 (3.3)	<0.001
Regular physical activity (≥mod intensity, %)	19 (0.6)	13.6 (2.3)	0.033
Presence of HTN (yes, %)	37.3 (0.8)	57.5 (3.6)	<0.001
Fasting serum glucose (≥126 mg/dL, %)	11.8 (0.5)	16.3 (2.9)	0.068
MetS (yes, %)	35.3 (0.7)	47.1 (3.8)	0.001

Data are presented as mean ± standard error (SE) or as % SE.

BMI = body mass index, BP = blood pressure, HTN = hypertension, IOP = intraocular pressure, MetS = metabolic syndrome.

sleep duration, showing a U-shaped association (Fig. 1). These trends were especially evident in obese individuals (Table 2). Collectively, these findings suggest that sleep disturbances may contribute to glaucoma, particularly in the obese population.

The association between sleep disturbances and glaucoma is possibly mediated by melatonin. Melatonin modulates electrical activity in the suprachiasmatic nucleus (SCN), the primary circadian pacemaker of the human brain, and is recognized as the most important natural substance controlling sleep and circadian rhythms.^[22] The SCN receives photic input via specialized signal transduction mechanisms sent by intrinsically photosensitive cells in the retina,^[23] so-called intrinsically photosensitive retinal ganglion cells (ipRGCs). ipRGC photoreceptors contain the pigment melanopsin, a newly described opsin that is involved not in image formation, but in nonvisual phototransduction to the SCN, and thereby in the synchronization of circadian rhythms.^[24–27] There is evidence that glaucoma involves the loss of ipRGCs, and may affect alterations in the retino-hypothalamic tract regardless of IOP.^[28,29] Retinal oxidative stress has been known as one of the factors promoting glaucomatous neurodegeneration.^[30] Glutamate is a major excitatory neurotransmitter in the central nervous system and the retina and has been found to be increased in glaucoma. Glutamate increases intracellular calcium levels, nitric oxide synthesis, free radical production, and mitochondrial dysregulation, which results in oxidative neuronal damage and ipRGC death in glaucoma.^[31–33] In this regard, the loss of ipRGCs in glaucoma may compromise circadian rhythms and regulation of sleep.^[34,35]

Besides its vital role in the regulation of sleep and the circadian system,^[22,36,37] melatonin has other important functions. In the central nervous system, melatonin protects neurons from oxidative stress,^[38] and it has been considered a candidate for

the treatment of neurodegenerative diseases.^[39–42] Melatonin also acts as an antioxidant in the retina, where it scavenges light-induced free radicals and inhibits the nitridergic pathway,^[43–46] thereby having a protective effect on the outer membranes of photoreceptors and reversing the effect of ocular hypertension on retinal function.^[47] Melatonin also directly and significantly reduces IOP, putatively through the MT3 receptor.^[48,49] Reports from various laboratories have correlated the daily onset of melatonin secretion with the onset of nocturnal sleepiness.^[50,51] In this regard, the association between short sleep duration and the prevalence of glaucoma observed in the current study may be the result of a reduction in melatonin release.

In this study, a U-shaped association of sleep duration with glaucoma was evident, particularly in obese individuals ($P=0.840$ in subjects with BMI <25 kg/m² and $P=0.036$ in subjects with BMI ≥25 kg/m²) (Table 2). Sleep duration also showed the U-shaped association with diabetic retinopathy.^[52] This may be

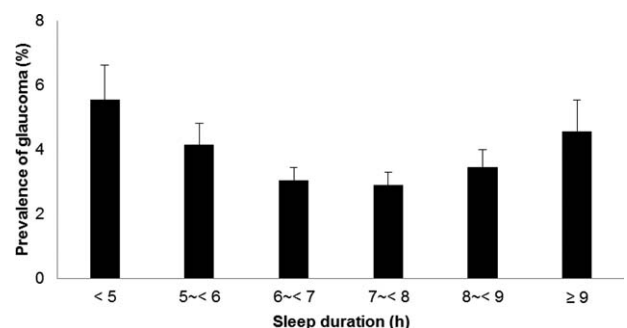


Figure 1. Prevalence of glaucoma according to sleep duration. Short and long sleep was associated with high prevalence of glaucoma (P for trend = 0.072).

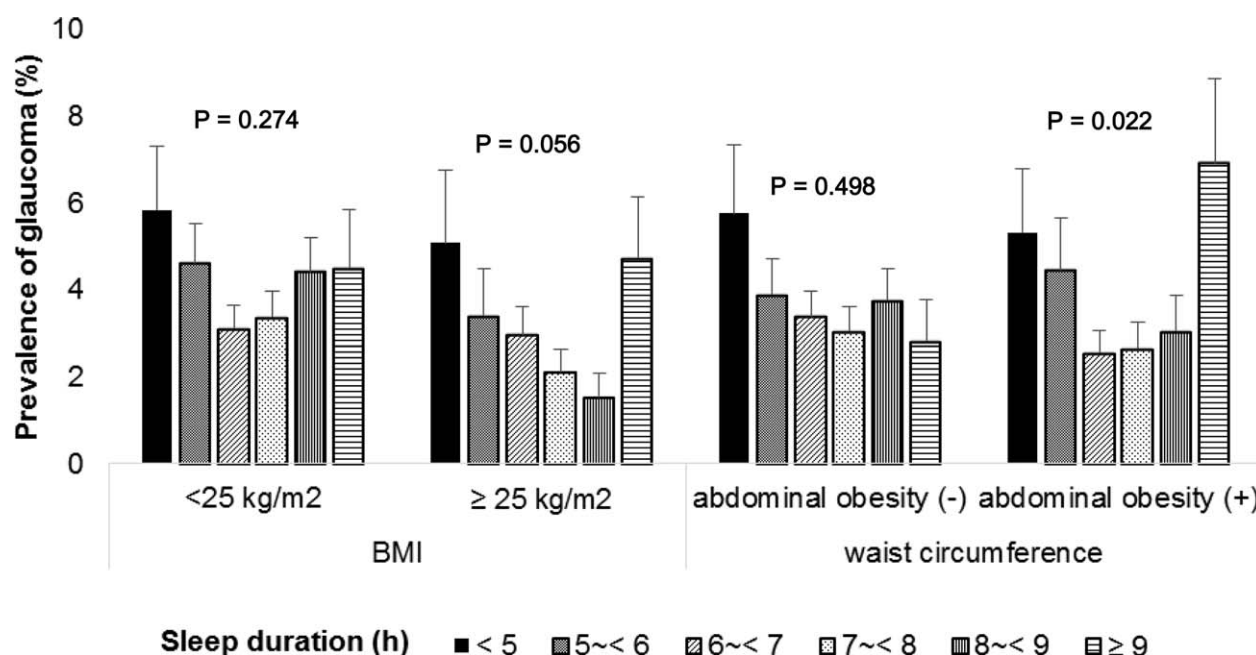


Figure 2. The relationships between sleep duration and the prevalence of glaucoma in subgroups based on body mass index and abdominal obesity. In the overweight subgroup, the prevalence of glaucoma was highest in subjects who slept less than 5 h per night, followed by those who slept 9 h or more, showing a U-shaped pattern (P for trend = 0.056), whereas no trend was observed in nonoverweight subjects ($P = 0.274$). In the patient subgroup with abdominal obesity, the prevalence of glaucoma was highest in subjects who slept 9 h or more, followed by those who slept less than 5 h, showing a similar U-shaped pattern (P for trend = 0.022). In contrast, there was no trend in the patient subgroup without abdominal obesity ($P = 0.499$).

Table 2
Multiple logistic regression analyses of the prevalence of glaucoma according to sleep duration.

Sleep duration	Total population			
	Model 1	Model 2	Model 3	Model 4
<7 h	1.16 (0.88, 1.53)	1.07 (0.81, 1.42)	1.07 (0.81, 1.41)	1.10 (0.83, 1.45)
7~<8 h	1	1	1	1
≥9 h	1.48 (0.92, 2.37)	1.22 (0.76, 1.97)	1.16 (0.72, 1.85)	1.16 (0.73, 1.85)
<i>P</i> for trend	0.218	0.671	0.765	0.710
Subgroup analyses				
BMI < 25 kg/m ²				
<7 h	0.99 (0.71, 1.37)	0.93 (0.67, 1.30)	0.91 (0.66, 1.27)	0.93 (0.67, 1.30)
7~<8 h	1	1	1	1
≥9 h	1.18 (0.62, 2.23)	0.96 (0.50, 1.86)	0.88 (0.47, 1.64)	0.86 (0.46, 1.60)
<i>P</i> for trend	0.872	0.919	0.815	0.840
BMI ≥ 25 kg/m ²				
<7 h	1.79 (1.08, 2.96)	1.57 (0.92, 2.67)	1.70 (1.00, 2.88)	1.75 (1.01, 3.01)
7~<8 h	1	1	1	1
≥9 h	2.58 (1.28, 5.23)	2.15 (1.04, 4.43)	2.28 (1.09, 4.79)	2.41 (1.15, 5.03)
<i>P</i> for trend	0.013	0.081	0.047	0.036
Abdominal obesity (-)				
<7 h	1.13 (0.77, 1.63)	1.07 (0.73, 1.55)	1.06 (0.73, 1.55)	1.08 (0.74, 1.57)
7~<8 h	1	1	1	1
≥9 h	0.84 (0.40, 1.75)	0.67 (0.32, 1.42)	0.64 (0.31, 1.33)	0.64 (0.30, 1.36)
<i>P</i> for trend	0.663	0.479	0.404	0.394
Abdominal obesity (+)				
<7 h	1.22 (0.78, 1.90)	1.09 (0.70, 1.70)	1.12 (0.71, 1.75)	1.15 (0.73, 1.81)
7~<8 h	1	1	1	1
≥9 h	2.56 (1.27, 5.14)	2.19 (1.08, 4.45)	2.14 (1.05, 4.37)	2.15 (1.07, 4.31)
<i>P</i> for trend	0.030	0.084	0.105	0.094

Model 1: unadjusted; Model 2: adjusted for age and sex; Model 3: adjusted for age, sex, smoking, drinking, exercise, education level, and household income; Model 4: adjusted for age, sex, smoking, drinking, exercise, education level, household income, hypertension, intraocular pressure, stress, and depression.

associated with the anti-obesogenic and weight-reducing effects of melatonin. Melatonin is the key molecule that integrates light cycles in the external environment and circadian changes in physiological and behavioral processes that are necessary for the maintenance of a healthy metabolism and for the optimization of energy balance and body weight regulation.^[32] Melatonin is responsible for the establishment of an adequate energy balance mainly via regulation of energy flow to and from energy stores and through the activation of brown adipose tissue.^[19] An absence or reduction in melatonin production, as occurs with age, in shift workers, or in those who are in illuminated environments during the night, induces insulin resistance, glucose intolerance, sleep disturbances, and metabolic circadian disorganization, all of which contribute to metabolic diseases, which, in a vicious cycle, negatively impact the circadian system, aggravating overall health and leading to obesity.^[19] The available evidence supports the suggestion that melatonin replacement therapy may ameliorate the abovementioned pathologies and restore the organism to a healthier state.^[19]

The reason for the significant association between long sleep duration and glaucoma is not clear. One possibility involves systemic nocturnal hypotension during sleep. Charlson et al^[53] reported that cumulative nocturnal hypotension predicted visual field loss in a cohort study. They found that the duration and magnitude of a decrease in nocturnal BP below daytime mean arterial pressure predicted progression of normal-tension glaucoma.^[53] Further prospective studies regarding sleep duration and the incidence of glaucoma are necessary to confirm our findings.

Our study was performed using KNHANES data, as that data is reliable, thorough, large-scale, and nationally representative. To the best of our knowledge, we are not aware of previous studies demonstrating the association between sleep duration and open angle glaucoma. However, there are certain limitations that should be noted. First, this was a cross-sectional study and the association discovered here may not imply a causal relationship. This study did not include measurements of the levels of melatonin in subjects' blood. Third, information on sleep duration was based on subjective, self-reported data; thus there may be a misclassification bias. Fourth, whether sleep duration is a useful indicator or a proxy for exposure to darkness is unclear. In addition to sleep duration per se, other factors related to sleep, including habitual timing of sleep, frequency of awakening during the night, nighttime lighting conditions, and sleep quality, may also influence melatonin release. Unfortunately, the self-reported questionnaire did not include categories about sleep quality, sleep disorder, or sleep fragmentation. To identify the effects of pure sleep duration or sleep quality on glaucoma, further prospective studies that include objective assessments of sleep duration and quality will be needed.

In conclusion, a U-shaped association existed between sleep duration and the prevalence of glaucoma. The trend was especially evident in overweight individuals. These findings suggest that approaches specific to individual sleep patterns and body types may be helpful in the management of glaucoma.

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References

- [1] Group CN-TGS. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. *Am J Ophthalmol* 1998;126:487–97.
- [2] Investigators, A., The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. *Am J Ophthalmol* 2000;130:429–40.
- [3] Lichter PR, Musch DC, Gillespie BW, et al. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. *Ophthalmology* 2001;108:1943–53.
- [4] Leske MC, Heijl A, Hussein M, et al. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. *Arch Ophthalmol* 2003;121:48–56.
- [5] Musch DC, Gillespie BW, Niziol LM, et al. Group CS Intraocular pressure control and long-term visual field loss in the Collaborative Initial Glaucoma Treatment Study. *Ophthalmology* 2011;118:1766–73.
- [6] Jean-Louis G, Zizi F, Lazzaro DR, et al. Circadian rhythm dysfunction in glaucoma: a hypothesis. *J Circadian Rhythms* 2008;6:1.
- [7] Mojon DS, Hess CW, Goldblum D, et al. Normal-tension glaucoma is associated with sleep apnea syndrome. *Ophthalmologica* 2002;216:180–4.
- [8] Mojon DS, Hess CW, Goldblum D, et al. Primary open-angle glaucoma is associated with sleep apnea syndrome. *Ophthalmologica* 2000;214:115–8.
- [9] Mabuchi F, Yoshimura K, Kashiwagi K, et al. High prevalence of anxiety and depression in patients with primary open-angle glaucoma. *J Glaucoma* 2008;17:552–7.
- [10] Agorastos A, Skevas C, Matthaei M, et al. Depression, anxiety, and disturbed sleep in glaucoma. *J Neuropsychiatry Clin Neurosci* 2013;25:205–13.
- [11] Feigl B, Mattes D, Thomas R, et al. Intrinsically photosensitive (melanopsin) retinal ganglion cell function in glaucoma. *Invest Ophthalmol Vis Sci* 2011;52:4362–7.
- [12] Wiechmann AF, Summers JA. Circadian rhythms in the eye: the physiological significance of melatonin receptors in ocular tissues. *Prog Retinal Eye Res* 2008;27:137–60.
- [13] Agorastos A, Huber CG. The role of melatonin in glaucoma: implications concerning pathophysiological relevance and therapeutic potential. *J Pineal Res* 2011;50:1–7.
- [14] Pescosolido N, Gatto V, Stefanucci A, et al. Oral treatment with the melatonin agonist agomelatine lowers the intraocular pressure of glaucoma patients. *Ophthalmic Physiol Opt* 2015;35:201–5.
- [15] Hardeband R, Madrid JA, Tan DX, et al. Melatonin, the circadian multioscillator system and health: the need for detailed analyses of peripheral melatonin signaling. *J Pineal Res* 2012;52:139–66.
- [16] Pandi-Perumal SR, Srinivasan V, Maestroni GJ, et al. Melatonin: nature's most versatile biological signal? *FEBS J* 2006;273:2813–38.
- [17] Reiter RJ, Tan DX, Galano A. Melatonin: exceeding expectations. *Physiology (Bethesda)* 2014;29:325–33.
- [18] Saarela S, Reiter RJ. Function of melatonin in thermoregulatory processes. *Life Sci* 1994;54:295–311.
- [19] Cipolla-Neto J, Amaral F, Afeche S, et al. Melatonin, energy metabolism, and obesity: a review. *J Pineal Res* 2014;56:371–81.
- [20] Kim S, Lee J, Lee J, et al. Prevalence of diabetes and impaired fasting glucose in Korea Korean National Health and Nutrition Survey 2001. *Diabetes Care* 2006;29:226–31.
- [21] Choi JA, Han K, Park Y-M, et al. Age-related association of refractive error with intraocular pressure in the Korea National Health and Nutrition Examination Survey. *PLoS One* 2014;9:e111879.
- [22] Czeisler CA, Duffy JF, Shanahan TL, et al. Stability, precision, and near-24-hour period of the human circadian pacemaker. *Science* 1999; 284:2177–81.
- [23] Berson DM, Dunn FA, Takao M. Phototransduction by retinal ganglion cells that set the circadian clock. *Science* 2002;295:1070–3.
- [24] Hattar S, Liao H-W, Takao M, et al. Melanopsin-containing retinal ganglion cells: architecture, projections, and intrinsic photosensitivity. *Science* 2002;295:1065–70.
- [25] Provencio I, Rodriguez IR, Jiang G, et al. A novel human opsin in the inner retina. *J Neurosci* 2000;20:600–5.
- [26] Cermakian N, Sassone-Corsi P. Environmental stimulus perception and control of circadian clocks. *Curr Opin Neurobiol* 2002;12:359–65.
- [27] Panda S, Nayak SK, Campo B, et al. Illumination of the melanopsin signaling pathway. *Science* 2005;307:600–4.

- [28] Schwartz M, London A. Glaucoma as a neuropathy amenable to neuroprotection and immune manipulation. *Prog Brain Res* 2008;173:375–84.
- [29] Walland MJ, Carassa RG, Goldberg I, et al. Failure of medical therapy despite normal intraocular pressure. *Clin Exp Ophthalmol* 2006;34:827–36.
- [30] Moreno MC, Campanelli J, Sande P, et al. Retinal oxidative stress induced by high intraocular pressure. *Free Radic Biol Med* 2004;37:803–12.
- [31] Kaushik S, Pandav S, Ram J. Neuroprotection in glaucoma. *J Postgrad Med* 2003;49:90.
- [32] Sucher NJ, Lei SZ, Lipton SA. Calcium channel antagonists attenuate NMDA receptor-mediated neurotoxicity of retinal ganglion cells in culture. *Brain Res* 1991;551:297–302.
- [33] Moreno MC, Sande P, Marcos HA, et al. Effect of glaucoma on the retinal glutamate/glutamine cycle activity. *FASEB J* 2005;19:1161–2.
- [34] Bailes HJ, Lucas RJ. Melanopsin and inner retinal photoreception. *Cell Mol Life Sci* 2010;67:99–111.
- [35] Drouyer E, Dkhissi-Benyahya O, Chiquet C, et al. Glaucoma alters the circadian timing system. *PLoS One* 2008;3:e3931.
- [36] Nowak J, Zawilska J. Melatonin and its physiological and therapeutic properties. *Pharm World Sci* 1998;20:18–27.
- [37] Leproult R, Van Onderbergen A, L'Hermite-Balériaux M, et al. Phase-shifts of 24-h rhythms of hormonal release and body temperature following early evening administration of the melatonin agonist agomelatine in healthy older men. *Clin Endocrinol* 2005;63:298–304.
- [38] Hardeland R. Antioxidative protection by melatonin. *Endocrine* 2005;27:119–30.
- [39] Reiter RJ. Oxidative damage in the central nervous system: protection by melatonin. *Prog Neurobiol* 1998;56:359–84.
- [40] Srinivasan V, Pandi-Perumal S, Mastroni G, et al. Role of melatonin in neurodegenerative diseases. *Neurotoxicity Res* 2005;7:293–318.
- [41] Srinivasan V, Pandi-Perumal S, Cardinali D, et al. Melatonin in Alzheimer's disease and other neurodegenerative disorders. *Behav Brain Funct* 2006;2:15.
- [42] Mayo JC, Sainz RM, Tan D-X, et al. Melatonin and Parkinson's disease. *Endocrine* 2005;27:169–78.
- [43] Osborne NN, Chidlow G, Nash MS, et al. The potential of neuroprotection in glaucoma treatment. *Curr Opin Ophthalmol* 1999;10:82–92.
- [44] Siu AW, Maldonado M, Sanchez-Hidalgo M, et al. Protective effects of melatonin in experimental free radical-related ocular diseases. *J Pineal Res* 2006;40:101–9.
- [45] Sáenz DA, Turjanski AG, Sacca GB, et al. Physiological concentrations of melatonin inhibit the nitridergic pathway in the Syrian hamster retina. *J Pineal Res* 2002;33:31–6.
- [46] Hardeland R, Balzer I, Poeggeler B, et al. On the primary functions of melatonin in evolution: mediation of photoperiodic signals in a unicell, photooxidation, and scavenging of free radicals. *J Pineal Res* 1995;18:104–11.
- [47] Belforte NA, Moreno MC, De Zavalía N, et al. Melatonin: a novel neuroprotectant for the treatment of glaucoma. *J Pineal Res* 2010;48:353–64.
- [48] Samples JR, Krause G, Lewy AJ. Effect of melatonin on intraocular pressure. *Curr Eye Res* 1988;7:649–53.
- [49] Serle JB, Wang R-F, Peterson WM, et al. Effect of 5-MCA-NAT, a putative melatonin MT3 receptor agonist, on intraocular pressure in glaucomatous monkey eyes. *J Glaucoma* 2004;13:385–8.
- [50] Åkerstedt T, Fröberg JE, Friberg Y, et al. Melatonin excretion, body temperature and subjective arousal during 64 hours of sleep deprivation. *Psychoneuroendocrinology* 1979;4:219–25.
- [51] Zhdanova IV, Wurtman RJ, Morabito C, et al. Effects of low oral doses of melatonin, given 2–4 hours before habitual bedtime, on sleep in normal young humans. *Sleep* 1996;19:423–31.
- [52] Jee D, Keum N, Kang S, et al. Sleep and diabetic retinopathy. *Acta Ophthalmol* 2016; [Epub ahead of print].
- [53] Charlson ME, de Moraes CG, Link A, et al. Nocturnal systemic hypotension increases the risk of glaucoma progression. *Ophthalmology* 2014;121:2004–12.