

SCIENTIFIC INVESTIGATIONS

A Nationwide Cross-Sectional Survey of Sleep-Related Problems in Japanese Visually Impaired Patients: Prevalence and Association with Health-Related Quality of Life

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Study Objectives: This questionnaire-based cross-sectional study was conducted (1) to estimate the prevalence of sleep-related problems, and (2) to explore factors associated with lower physical/mental quality of life (QOL), particularly addressing sleep-related problems among Japanese visually impaired people.

Methods: This nationwide questionnaire-based survey was administered to visually impaired individuals through the Japan Federation of the Blind. Visually impaired individuals without light perception (LP) (n = 311), those with LP (n = 287), and age-matched and gender-matched controls (n = 615) were eligible for this study. Study questionnaires elicited demographic information, and information about visual impairment status, sleep-related problems, and health-related quality of life.

Results: Visually impaired individuals with and without LP showed higher prevalence rates of irregular sleep-wake patterns and difficulty maintaining sleep than controls (34.7% and 29.4% vs. 15.8%, 60.1% and 46.7% vs. 26.8%, respectively; p < 0.001). These sleep-related problems were observed more frequently in visually impaired individuals without LP than in those with LP. Non-restorative sleep or excessive daytime sleepiness was associated with lower mental/physical QOL in visually impaired individuals with LP and in control subjects. However, visually impaired individuals without LP showed irregular sleep-wake pattern or difficulty waking up at the desired time, which was associated with lower mental/physical QOL.

Conclusions: Sleep-related problems were observed more frequently in visually impaired individuals than in controls. Moreover, the rates of difficulties were higher among subjects without LP. Sleep-related problems, especially circadian rhythm-related ones, can be associated with lower mental/physical QOL in visually impaired individuals without LP.

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INTRODUCTION

Visually impaired individuals are likely to have any of several comorbid mental/physical disorders including diabetes mellitus, hypertension, cognitive impairment, and depression/ anxiety.¹⁻⁶ The severity of these mental/physical disorders is reportedly correlated with visual impairment.¹⁻⁹ Therefore, those individuals might be at risk for lower health-related quality of life (QOL).⁷⁻¹⁰

Sleep-related problems have been observed frequently in visually impaired individuals.^{11–15} Reportedly, especially in people without light perception (LP), inhibited transmission of light signals to the suprachiasmatic nuclei might cause sleep-related problems because of external desynchronization of the biological clock.^{16,17} Indeed, the rate of circadian-related sleep-wake disorders is likely to be higher among visually impaired individuals without LP than among those with LP.¹² In Japan, no large nationwide study of this subject has ever been reported. The actual prevalence of sleep-related problems among visually impaired individuals in Japan remains unclear.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Although earlier studies have demonstrated that sleep-related problems including circadian rhythm sleep-wake disorder are more prevalent in visually impaired individuals without light perception (LP), few studies have examined the prevalence of sleep-related problems including circadian rhythm sleep–wake disorder, emphasizing the presence/absence of LP. Furthermore, the association of sleep-related problems with physical/ mental QOL has not been investigated among visually-impaired individuals to date.

Study Impact: Irregular sleep-wake pattern, difficulty maintaining sleep and excessive daytime sleepiness were observed more frequently in the Japanese visually-impaired individuals than in a control group; the relative frequencies of these problems were higher in those without LP. Furthermore, the association of sleep-related problems possibly manifesting circadian rhythm sleep–wake disorder to mental/physical QOL was greater, especially in visually impaired individuals without LP.

Sleep-related problems are known to be intimately associated with physical and psychological dysfunction in the general population.^{18–22} Therefore, sleep-related problems can be regarded as a major risk factor for lower QOL among visually impaired individuals. Nevertheless, no study investigating the association between sleep-related problems and physical/ mental QOL among visually impaired individuals has ever been reported.

Considering the issues described above, the aims of this questionnaire-based cross-sectional study were to (1) estimate the prevalence of sleep-related problems among Japanese visually impaired people, particularly addressing the presence/ absence of LP, and to (2) explore the association between sleep-related problems and physical/mental QOL among this population.

METHODS

Setting and Survey Procedure

The protocol of the current study was reviewed and approved by the Research Ethics Committee of Tokyo Medical University (approved number: 2474). Written informed consent was obtained from the study participants and/or their family members.

The study was conducted during October 2013–November 2013 with the cooperation of a non-profit organization, the Japan Federation of the Blind (JFB). The JFB is a nationwide organization comprising 61 affiliated organizations including approximately 50,000 blind or visually impaired individuals in Japan. The organization provides employment support, audio and Braille libraries, social and medical information, and various support services to these individuals.

First, we distributed information about this study to the 61 affiliated organizations through the JFB and asked for their cooperation. Next, we mailed questionnaires to the affiliated organizations which agreed to participate in the study. These affiliated organizations distributed a letter soliciting cooperation in our study, which included an informed consent form, the study questionnaires in Braille and regular text, and a return envelope. We also distributed questionnaires with a consent form to age-matched and gender-matched controls. It did not include items related to visual impairment. Individuals who agreed to participate in the study completed the questionnaires and returned them by mail to the research team.

Participants

Visually Impaired Individuals

Individuals with severe visual impairment who had a Grade 1 (0.01 or less visual acuity in bilateral eyes) or Grade 2 ([1] monocular blindness and 0.02 or less vision in the other eye, or [2] 0.02 or less vision in bilateral eyes) disability were recruited for the study. Of 61 affiliated organizations, 60 agreed to cooperate in the study. The organizations randomly selected a total of 1,200 visually impaired individuals according to the stratified random sampling method²³ in which the strata were formed based on gender and age (20s, 30s, 40s, 50s, 60s, and older). By this process, no more than 20 samples were selected randomly by each affiliated organization: two

women and two men were selected from each age stratum. Among 1,200 eligible individuals, 631 agreed to participate in the study and returned the study questionnaire (response rate: 52.3%). Of the 631 participants, 33 were excluded because either their gender, age, or presence/absence of LP was not provided. Consequently, data of 598 participants were analyzed (**Figure 1**).

Controls

For the control group, a total of 1,200 individuals without visual impairment were recruited similarly to the recruiting of the visually impaired individuals, except that we enlisted staff members working in the JFB or their family members. Gender, age, and residential area were matched to the individuals with visual impairment. Among 1,200 eligible individuals, 622 agreed to participate in the study and completed the questionnaires (response rate: 51.8%). Of the 622 participants, 7 were excluded because of incomplete information related to gender or age. Consequently, data of 615 participants in the control group were used for analyses (**Figure 1**).

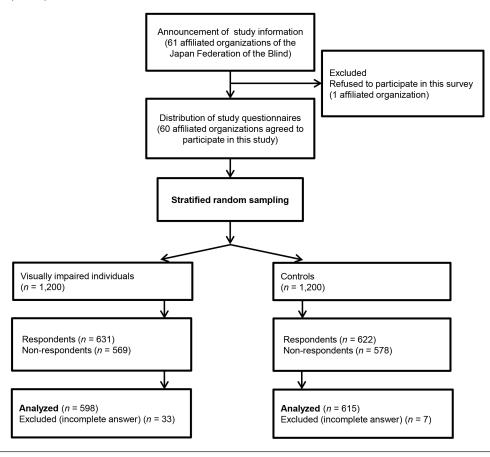
Measurements

The questionnaire asked for the following basic information: age, gender (female/male), employment status (employed/unemployed), residential status (living alone/living with family member/living in a nursing home), body mass index (BMI), exercise habits (having regularly scheduled [two times or more per week] exercise more than 30 min maintained for over a year)²⁴ (yes/no), presence of a currently treated disease (yes/no), frequency of alcohol use (daily/occasionally/never), frequency of smoking (daily/occasionally/never), and total walking-time per day (> 60 min min/30–60 min/< 30 min).²⁵ For individuals with visual impairment, the questionnaire asked for the following additional information: visual status (visual impairment/ blindness), light perception (with/without), cause of visual impairment (congenital/acquired), age of the onset of visual impairment, and morbidity length of visual impairment. Based on the obtained information related to light perception, visually impaired individuals were classified into the following two groups: visually impaired individuals without LP (n = 311) and visually impaired individuals with LP (n = 287).

Sleep disturbances experienced during the prior month were evaluated based on "yes" or "no" responses to the following six questions:

- 1. Irregular sleep-wake pattern: Do you have an irregular sleep-wake pattern including progressive drifting of sleep onset and offset?
- 2. Difficulty initiating sleep: Do you have difficulty falling asleep at night?
- 3. Difficulty maintaining sleep: Do you wake up during the night after you fall asleep and have difficulty getting back to sleep?
- 4. Non-restorative sleep: Do you feel refreshed and get sound sleep after waking up in the morning?
- 5. Difficulty waking up at a desired time: Do you have difficulty waking up at a desired time in the morning?
- 6. Excessive daytime sleepiness: Do you feel excessively sleepy during the daytime?

Figure 1—Flow of participants.



Questions 1 and 5 were set to detect circadian-rhythm-related sleep disorder according to previous reports.^{26,27}

The standardized 8-item Short Form Health Survey (SF-8) of the Medical Outcomes Study²⁸ was used to assess health-related quality of life. The SF-8 measures 8 health domains: vitality, social functioning, mental health condition, emotional state, general health, physical functioning, physical state, and bodily pain. For each domain a score of 0 to 100 was assigned, with higher scores indicating better health in that domain. Scores for the 8 items were standardized based on the 2007 Japanese population norm having a distribution with a mean of 50 and a standard deviation of 10.²⁸ The physical component score (PCS) and the mental component score (MCS) of the SF-8 respectively represent physical QOL and mental QOL. In this study, lower PCS and MCS were defined as scores below the mean scores of the Japanese general population: 49.84 for PCS and 50.09 for MCS²⁸ according to the user's manual.²⁹

Statistical Analysis

To analyze differences in demographic characteristics, Student *t*-test and a one-way analysis of variance (ANOVA) followed by Bonferroni post hoc test were applied for continuous variables. The χ^2 test with residual analysis for categorical variables was applied for the rate of sleep disturbances and health-related QOL between the groups of visually impaired individuals and controls, and among the groups of visually impaired individuals with LP, without LP, and controls. Factors associated with lower PCS and MCS were examined using a series of logistic regression analyses. Age at the onset of visual impairment and morbidity length of visual impairment were continuous variables. Age was categorized as younger (20–39 years), middle age (40–59 years), and elderly (\geq 60 years). The body mass index was categorized dichotomously at BMI \geq 25 kg/m².³⁰ All variables were examined initially in univariate models. To control for confounding factors and to ascertain the main correlates, we subsequently conducted multivariate logistic regression analyses for all variables showing a significant correlation in the univariate models. Statistical tests of estimated odds ratios were based on Wald statistics. These statistical analyses were conducted using software (Statistical Package for the Social Sciences, SPSS, ver. 22.0J; IBM SPSS, Inc., Tokyo, Japan).

RESULTS

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Differences in Demographic Characteristics and Visual Impairment Information among Visually Impaired Individuals with/without LP and Control Subjects

Table 1 presents demographic characteristics and information related to the visual impairment of the participants. The visually impaired individuals were significantly older than controls (p < 0.001) with a small effect size ($\eta^2 = 0.02$). Their body mass

Table 1—Demographic characteristics of the participants.

Variables	Visually impaired individuals without light perception (n = 311)	Visually impaired individuals with light perception (n = 287)	Controls (n = 615)	р	Effect size	
Age (years), mean ± SD	60.7 ± 13.0**	59.1 ± 13.0**	56.0 ± 13.7	< 0.001	η ² = 0.02	
Younger (20–39)	24 (7.7)	22 (7.7)	85 (13.8)**	< 0.001	V = 0.13	
Middle (40-59)	82 (26.4)	100 (34.8)	251 (40.8)**			
Elderly (≥ 60)	205 (65.9)*	165 (57.5)	279 (45.4)			
Gender						
Female	108 (34.7)	122 (42.5)	403 (65.2)**	< 0.001	V = 0.27	
Male	203 (65.3)**	165 (57.5)**	215 (34.8)			
Employment status						
Employed	215 (69.1)	186 (64.8)	425 (69.6)	0.339		
Unemployed	96 (30.9)	101 (35.2)	186 (30.4)			
Body mass index (kg/m ²)	23.3 ± 3.6**	22.9 ± 3.8**	22.1 ± 3.1	< 0.001	η ² = 0.02	
Visual status						
Visual impairment	2 (0.6)	162 (56.4)**	-	< 0.001	V = 0.86	
Blindness	309 (99.4)**	125 (43.6)	-			
Cause of visual impairment						
Congenital	122 (39.7)	131 (46.6)	_	0.102		
Acquired	185 (99.4)	150 (43.6)	_			
Age at the onset of visual impairment	14.3 ± 17.2	19.0 ± 21.8	_	0.005	<i>r</i> = 0.12	
Morbidity length of visual impairment	46.2 ± 19.0	40.0 ± 21.5	_	< 0.001	<i>r</i> = 0.16	

Data are expressed as mean \pm standard deviation or number of subjects (%). V = Cramer's V; η^2 = Partial Eta squared. **p < 0.01; *p < 0.05.

index was higher than that of the control subjects (p = 0.005). Visually impaired individuals without LP reported significantly earlier onset of visual impairment and longer morbidity duration of impairment than those with LP (p < 0.001).

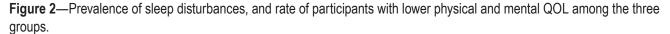
Conditions of Sleep-Related Problems and Health-Related Quality of Life

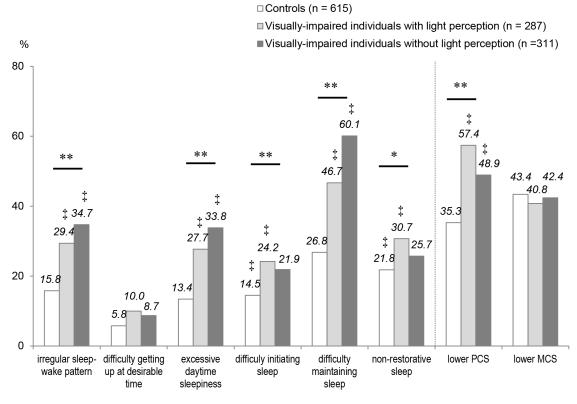
The rates of sleep-related problems of visually impaired individuals and controls (Figure 2) were compared. Results show that visually impaired individuals had significantly higher rates of the following disturbances: irregular sleep-wake pattern $(31.8\%, \chi^2 = 43.95, p < 0.001, \phi = 0.188)$, difficulty maintaining sleep (53.1%, $\chi^2 = 90.14$, p < 0.001, $\varphi = 0.269$), excessive daytime sleepiness (30.4%, $\chi^2 = 52.56$, p < 0.001, $\phi = 0.205$), difficulty initiating sleep (22.7%, $\chi^2 = 13.90$, p < 0.001, $\phi = 0.105$), and non-restorative sleep (28.0%, $\chi^2 = 13.90$, p < 0.001, $\varphi = 0.105$). Comparison of the rates between visually impaired individuals without LP, with LP, and the controls revealed that both visually impaired individuals with and without LP showed a higher rate of irregular sleep-wake pattern ($\chi^2 = 47.26$, p < 0.001, Cramer's V = 0.197), difficulty maintaining sleep ($\chi^2 = 103.12$, p < 0.001, Cramer's V = 0.217), and excessive daytime sleepiness ($\chi^2 = 57.37$, p < 0.001, Cramer's V = 0.217). In addition, the rate of non-restorative sleep and difficulty initiating sleep were higher in visually impaired individuals with LP and were lower in the controls $(\chi^2 = 8.72, p = 0.013, Cramer's V = 0.085; \chi^2 = 14.99, p = 0.001,$ Cramer's V = 0.111, respectively). No significant difference was found among the three groups in terms of difficulty waking up at a desired time ($\chi^2 = 5.83$, p = 0.054, $\phi = 0.069$).

Figure 2 also presents the rates for lower PCS and MCS. The rate for lower PCS was significantly higher for visually impaired participants than for controls ($\chi^2 = 38.61$, p < 0.001, $\varphi = 0.176$). The rate was also higher for visually impaired participants with and without LP than for control subjects ($\chi^2 = 43.13$, p < 0.001, Cramer's V = 0.188). Regarding rates for lower MCS, no significant difference was found among the three groups ($\chi^2 = 0.54$, p = 0.463, $\varphi = -0.021$).

Factors Associated with Lower Mental Quality of Life

Among the visually impaired individuals without LP, univariate logistic regression analyses revealed that five items were significantly associated with lower MCS: irregular sleep-wake pattern, difficulty initiating sleep, difficulty maintaining sleep, non-restorative sleep, and excessive daytime sleepiness. Multiple logistic regression analysis incorporating these items revealed that irregular sleep-wake pattern and non-restorative sleep were significantly associated with lower MCS. In those with LP, univariate logistic regression analyses revealed that five items were significantly associated with lower MCS: BMI $(\geq 25 \text{ kg/m}^2)$, irregular sleep-wake pattern, difficulty maintaining sleep, non-restorative sleep, and excessive daytime sleepiness. Multiple logistic regression analysis using these items revealed that non-restorative sleep, daytime sleepiness, and BMI ($\geq 25 \text{ kg/m}^2$) were significantly associated with lower MCS. Regarding the controls, univariate logistic regression analyses revealed that eight items were significantly associated with lower MCS: older age (≥ 60 years), lack of exercise habits, irregular sleep-wake pattern, difficulty initiating sleep,





PCS, physical component score; MCS, mental component score. Lower PCS and MCS were defined respectively as \leq 49.8 and \leq 50.5 based on average values of the Japanese normative data. **p < 0.001 and *p < 0.05 in comparison between the visually impaired individuals and the control subjects. $\pm p < 0.05$ in comparison among the visually impaired individuals without light perception, those with light perception, and the control subjects (residual error \geq 1.96).

difficulty maintaining sleep, difficulty waking up at a desired time, non-restorative sleep and excessive daytime sleepiness. Multivariate logistic regression analysis using these items revealed that irregular sleep-wake patterns, difficulty maintaining sleep, non-restorative sleep, and older age (≥ 60 years) were significantly associated with lower MCS (**Table 2**).

Factors Associated with Lower Physical Quality of Life

In visually impaired individuals without LP, univariate logistic regression analyses revealed that 8 items were significantly associated with lower PCS: cause of visual impairment, presence of disease currently treated, irregular sleep-wake pattern, difficulty initiating sleep, difficulty maintaining sleep, difficulty waking up at a desired time, non-restorative sleep and excessive daytime sleepiness. Multivariate logistic regression analysis revealed that irregular sleep-wake pattern, difficulty waking up at a desired time, cause of visual impairment, and disease currently treated were associated significantly with lower PCS. In those with LP, univariate logistic regression analyses revealed that seven items were associated significantly with lower PCS: cause of visual impairment, BMI ($\geq 25 \text{ kg/m}^2$), presence of disease currently treated, irregular sleep-wake pattern, difficulty maintaining sleep, difficulty waking up at a desired time, and daytime sleepiness. Multivariate logistic regression analysis revealed that daytime sleepiness, cause of visual impairment, and BMI ($\geq 25 \text{ kg/m}^2$) appeared as significantly associated factors.

Regarding the controls, univariate logistic regression analyses revealed that 8 items were associated significantly with lower PCS: presence of disease currently treated, lack of exercise habits, irregular sleep-wake pattern, difficulty initiating sleep, difficulty maintaining sleep, difficulty waking up at a desired time, non-restorative sleep, and excessive daytime sleepiness. Multivariate logistic regression analysis revealed that difficulty initiating sleep, non-restorative sleep, excessive daytime sleepiness, presence of disease currently treated, and lack of exercise habits were significantly associated with lower PCS (**Table 3**).

DISCUSSION

This nationwide survey was the first ever reported to estimate the prevalence of sleep-related problems and to clarify the association between sleep-related problems and health-related QOL in a large sample of Japanese visually impaired individuals. Results show that the rate of sleep-related problems, including irregular sleep-wake pattern, difficulty initiating sleep, difficulty maintaining sleep, nonrestorative sleep, and excessive daytime sleepiness, were significantly higher in visually impaired individuals than in controls. Regarding QOL, 48.9% to 57.4% of visually impaired participants scored as a having lower physical QOL, which is much higher than the rate for the general population (31.3%).³¹

Table 2—Factors associated with lower mental quality	y of life.
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	Visually impaired individuals without light perception (n = 311)			Visually impaired individuals with light perception (n = 287)			Controls (n = 615)		
Factors	AOR	(95%CI)	р	AOR	(95%CI)	р	AOR	(95%CI)	р
Demographic variables									
Age (years) Younger (20–39) Middle (40–59) Older (≥ 60)							1 0.48	(0.34–0.69)	< 0.001
Body mass index (kg/m ²) < 25 ≥ 25				1 0.45	(0.25–0.83)	0.011	0.40	(0.04-0.00)	< 0.00 I
Visual status Visual impairment				0.43	(0.23-0.03)	0.011	_		
Blindness							-		
Cause of visual impairment Congenital Acquired									
Disease currently treated No Yes									
Exercise habits Yes No									
Sleep problems Irregular sleep-wake pattern No Yes	1.00 1.80	(1.07–3.02)	0.027				1 2.30	(1.38–3.85)	0.001
Difficulty initiating sleep No Yes		(, , , , , , , , , , , , , , , , , , ,						(, , , , , , , , , , , , , , , , , , ,	
Difficulty maintaining sleep No Yes							1 2.02	(1.35–3.03)	0.001
Difficulty waking up at a desired time No Yes									
Non-restorative sleep No Yes	1.00 3.87	(2.17–6.91)	< 0.001	1 1.87	(1.05–3.32)	0.033	1 2.42	(1.56–3.75)	< 0.001
Excessive daytime sleepiness No Yes	0.01	(0.01)	0.001	1 2.24	(1.23-4.06)	0.008		(5.001

The data were controlled for gender, age at the onset of visual impairment, morbidity length of visual impairment, employment status, residential status, alcohol use, smoking habits and total walking time per day. AOR = adjusted odds ratio, CI = confidence interval.

In this study, the rate of individuals reporting irregular sleepwake pattern, difficulty maintaining sleep and daytime sleepiness were significantly higher in visually impaired participants than in control subjects. Consistent with previous reports,^{11,12} the rates were higher especially in visually impaired individuals without LP. Reportedly, visually impaired individuals without LP are more likely to have an abnormal melatonin rhythm because of the inhibited transmission of a light signal, which might contribute to the occurrence of irregular sleep-wake patterns.^{15,16,21,26,27,32} In addition, misaligned rhythms of core body temperature or cortisol secretion can be explanations for their sleep-related difficulties.^{16,33} Furthermore, the dysregulated circadian rhythm negatively affects their ability to sleep and to maintain daytime vigilance.^{14,16,21,32}

In the present study, sleep-related problems such as nonrestorative sleep and excessive daytime sleepiness were found to be associated with lower mental and physical QOL in visually impaired individuals with LP and the controls. Several

	Visually impaired individuals without light perception (n = 311)				y impaired ind ht perception (Controls (n = 615)		
Factors	AOR	(95%CI)	р	AOR	(95%CI)	р	AOR	(95%CI)	р
Demographic variables									
Age (years) Younger (20–39) Middle (40–59) Older (≥ 60)									
Body mass index (kg/m²) < 25				1.00	<i></i>				
≥ 25				1.94	(1.06–3.55)	0.033			
Visual status Visual impairment Blindness							-		
Cause of visual impairment Congenital	1.00			1.00			_		
Acquired	1.76	(1.07–2.89)	0.026	1.86	(1.12–3.09)	0.016	-		
Disease currently treated									
No Yes	1.00 2.65	(1.49–4.69)	0.001				1.00 2.62	(1.52–4.51)	0.00
Exercise habits Yes No							1.00 1.51	(1.04–2.19)	0.03
Sleep problems									
Irregular sleep-wake pattern									
No	1.00								
Yes	1.98	(1.19–3.32)	0.009						
Difficulty initiating sleep									
No							1.00	(4.0.40.00)	0.00
Yes							2.02	(1.24–3.30)	0.00
Difficulty maintaining sleep No Yes									
Difficulty waking up at a desired time									
No	1.00								
Yes	4.00	(1.06–15.04)	0.04						
Non-restorative sleep No Yes							1.00 1.96	(1.27–3.03)	0.00
Excessive daytime sleepiness								. ,	
No				1.00			1.00		
Yes				1.94	(1.07–3.51)	0.029	2.00	(1.19–3.34)	0.00

Table 3—Factors associated with lower physical quality of li	ife.
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The data were controlled for gender, age at the onset of visual impairment, morbidity length of visual impairment, employment status, residential status, alcohol use, smoking habits and total walking time per day. AOR = adjusted odds ratio, CI = confidence interval.

reports have described that sleep disturbances or excessive daytime sleepiness are associated with an increased risk not only for psychiatric disorders including depression but also for decreased psychomotor performance such as cognitive function and short-term memory.^{34–36} Therefore, the present results of the association between these sleep disturbances and lower mental/physical QOL are reasonable.

Irregular sleep-wake pattern and difficulty waking up at desired time, each of which is suggestive of the presence of

circadian rhythm-related problems, were extracted as factors associated with lower mental/physical QOL, especially in visually impaired individuals without LP. Among them, nonrestorative sleep was associated only with lower physical QOL. A possible explanation for the association between circadianrhythm-related problems and lower mental/physical QOL observed only in the visually impaired individuals without LP is that external desynchronization might occur in this population. Reportedly, visually impaired individuals with circadian rhythm sleep–wake disorders exhibit a delayed circadian phase (e.g., melatonin phase range = 07.20-14.25 h)¹⁵ or free-running circadian rhythms (e.g., tau range = 24.13-24.79 h).^{15,16,21,27} Under these circumstances, their effort to stay awake during the daytime develops desynchronization-related mental and physical symptoms such as depression, fatigue or headache, possibly leading to lower mental/physical QOL.^{37,38} This fact might explain that circadian rhythm-related sleep problems were associated with lower mental and physical QOL especially in visually impaired individuals without LP. Consequently, in visually impaired individuals with LP, the factors associated with lower QOL were similar to the controls except for the cause of visual impairment. For people without LP, circadian rhythm-related problems were associated with lower QOL.

Several limitations of this study are noteworthy. First, the rate of individuals having irregular sleep-wake pattern was higher than the rate in a previous study (31.8% vs. 13% to 26%).^{12,13} A similar tendency was observed for other sleep-related problems. A possible reason for this discrepancy is that sleep-related problems were evaluated in the present study using a non-validated and self-administered questionnaire, whereas earlier studies used validated questionnaires or a telephone interview.^{12,13} Lack of detailed information related to participants' sleep habits, which is obtainable using sleep logs, did not allow for a more comprehensive exploration of the relation between sleep-related problem severity and health-related QOL. Furthermore, whether nocturnal sleep disturbances are attributable to circadian rhythm sleep-wake disorders or to primary insomnia could not be determined. Similarly, non-restorative sleep assessed by the question 4 might reflect morning sleep inertia. To clarify these issues, clarifying sleep-related problems using a structured interview together with sleep log records of two weeks or more would be necessary. Furthermore, shift-workers could not be excluded because the current questionnaire did not assess respondents' work schedules. Second, the accuracy of information about participants' light perception is questionable because self-reporting was used to assess the degree and nature of impairment. For example, detailed information about the nature of visual impairments determining ocular or cortical blindness was unobtainable. Although some results of studies have shown that self-reported data related to visual disability show at least moderate agreement with data from an objective assessment, 39,40 objective data (i.e., ophthalmologic measurements such as electroretinographic testing) are preferred. Third, the response ratio to the current survey was no higher than 52.3%. Unfortunately, although the information of non-responders was not obtained in this survey, potential volunteer bias must be considered.

In conclusion, visually impaired individuals had more prevalent sleep-related problems than the control subjects had. Particularly, the visually impaired individuals without LP reported higher prevalence of irregular sleep–wake patterns, difficulty maintaining sleep, and daytime sleepiness than those with LP. Sleep-related problems were associated with lower physical and mental QOL in both the visually impaired and the control subjects. However, an irregular sleep-wake pattern and difficulty waking up at a desired time were associated with lower physical QOL only in visually impaired individuals without LP. These sleep disturbances might be caused by a circadian rhythm sleep-wake disorder. Future studies should include a prospective follow-up study to clarify causal relations between physical QOL and circadian rhythm sleep-wake disorders.

ABBREVIATIONS

BMI, body mass index JFB, the Japan Federation of the Blind LP, light perception MCS, the mental component score PCS, the physical component score QOL, quality of life

REFERENCES

- Crews JE, Jones GC, Kim JH. Double jeopardy: the effects of comorbid conditions among older people with vision loss. J Visual Impair Blin 2006;100:824–48.
- Ong SY, Cheung CY, Li X, et al. Visual impairment, age-related eye diseases, and cognitive function: the Singapore Malay Eye Study. Arch Ophthalmol 2012;130:895–900.
- van der Aa HPA, Comijs HC, Penninx BWJH, van Rens GHMB, van Nispen RMA. Major depressive and anxiety disorders in visually impaired older adults. Invest Ophthalmol Vis Sci 2015;56:849–54.
- Salive ME, Gurainik J, Glynn RJ, Christen W, Wallace RB, Ostfeld AM. Association of visual impairment with mobility and physical function. J Am Geriatr Soc 1994;42:287–92.
- Haymes SA, Johnston AW, Heyes AD. Relationship between vision impairment and ability to perform activities of daily living. Ophthalmic Physiol Opt 2002;22:79–91.
- Lam BL, Christ SL, Zheng DD, et al. Longitudinal relationships among visual acuity and tasks of everyday life: the Salisbury Eye Evaluation Study. Invest Ophthalmol Vis Sci 2013;54:193–200.
- Crew JE, Chou CF, Zhang X, Zack MM, Saaddine JB. Health-related quality of life among people aged ≥ 65 years with self-reported visual impairment: findings from the 2006–2010 behavioral risk factor surveillance system. Ophthalmic Epidemiol 2014;21:287–96.
- Chia EM, Wang JJ, Rochtchina E, Smith W, Cumming RR, Mitchell P. Impact of bilateral visual impairment on health-related quality of life: the Blue Mountains Eye Study. Invest Ophthalmol Vis Sci 2004;45:71–6.
- Lisboa R, Chun YS, Zangwill LM, et al. Association between rates of binocular visual field loss and vision-related quality of life in patients with glaucoma. JAMA Ophthalmol 2013;131:486–94.
- Medeiros FA, Gracitelli CPB, Boer ER, Weinreb RN, Zangwill LM, Rosen PN. Longitudinal changes in quality of life and rates of progressive visual field loss in glaucoma patients. Ophthalmology 2015;122:293–301.
- 11. Tabandeh H, Lockly SW, Buttery R, et al. Disturbance of sleep in blindness. Am J Ophthalmol 1998;126:707–12.
- Warman GR, Pawley MDM, Bolton C, et al. Circadian-related sleep disorders and sleep medication use in the New Zealand blind population: an observational prevalence survey. PLoS One 2011;6:e22073.
- Leger D, Guilleminault C, Defrance R, Domont A, Paillard M. Prevalence of sleep/wake disorders in persons with blindness. Clin Sci 1999;97:193–9.
- Leger D, Guilleminault C, Santos C, Paillard M. Sleep/wake cycles in the dark: sleep recorded by polysomnography in 26 totally blind subjects compared to controls. Clin Neurophysiol 2002;113:1607–14.
- Lockley SW, Skene DJ, Butler LJ, Arendt J. Sleep and activity rhythms are related to circadian phase in the blind. Sleep 1999;22:616–23.
- Lockley SW, Arendt J, Skene DJ. Visual impairment and circadian rhythm disorders. Dialogues Clin Neurosci 2007;9:301–14.
- Schmoll C, Lascaratos G, Dhillon B, Skene D, Riha RL. The role of retinal regulation of sleep in health and disease. Sleep Med Rev 2011;15:107–13.

- Hayakawa T, Uchiyama M, Kamei Y, et al. Clinical analyses of sighted patients with non-24-hour sleep–wake syndrome: a study of 57 consecutively diagnosed cases. Sleep 2005;28:945–52.
- Scheer FAJL, Hilton MF, Mantzoros CS, Shea SA. Adverse metabolic and cardiovascular consequences of circadian misalignment. Proc Natl Acad Sci U S A 2009;106:4453–58.
- Buxton OM, Cain SW, O'Connor SP, et al. Metabolic consequences in humans of prolonged sleep restriction combined with circadian disruption. Sci Transl Med 2012;4:129ra43.
- Lockley SW, Dijk DJ, Kosti O, Skene DJ, Arendt J. Alertness, mood and performance rhythm disturbances associated with circadian sleep disorders in the blind. J Sleep Res 2008;17:207–16.
- Furihata R, Uchiyama M, Takahashi S, et al. The association between sleep problems and perceived health status: a Japanese nationwide general population survey. Sleep Med 2012;13:831–7.
- Noel CW, Fung H, Srivastava R, et al. Visual impairment and unmet eye care needs among homeless adults in a Canadian city. JAMA Ophthalmol 2015;133:455–60.
- Ministry of Health, Labour and Welfare. Exercise guidelines for good health 2006, (in Japanese). Retrieved May 26, 2015, from http://www.mhlw.go.jp/ bunya/kenkou/undou01/pdf/data.pdf
- Ministry of Health, Labour and Welfare. Japanese official physical activity guidelines for health promotion 2013, (in Japanese). Retrieved May 26, 2015, from http://www.mhlw.go.jp/sft/houdo u/2r9852000002xpleatt/2r9852000002xpqt.pdf
- Lockley SW, Skene DJ, Arendt J, Tabandeh H, Bird AC, Defrance R. Relationship between melatonin rhythms and visual loss in the blind. J Clin Endocrinol Metab 1997;82:3763–70.
- Flynn-Evans EE, Tabandeh H, Skene DJ, Lockley SW. Circadian rhythm disorders and melatonin production in 127 blind women with and without light perception. J Biol Rhythms 2014;29:215–24.
- Fukuhara S, Suzukamo Y, eds. Manual of the SF-8 Japanese Version, (in Japanese). Kyoto: Institute for Health Outcomes and Process Evaluation Research, 2004.
- Ware JE Jr. SF-36 Health Survey Update. In: Maruish MM, eds. The use of psychological testing for treatment planning and outcome assessment. New Jersey: Lawrence Erlbaum Associates, 2004:693–718.
- World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO consultation (WHO technical report series 894). Geneva, Switzerland: World Health Organization, 2000.
- Mori K, Kawano Y, Tada Y, et al. Relationship of dietary intake and lifestyle factors to health-related quality of life in the community-dwelling elderly. J Nutr Sci Vitaminol 2010;56:364–71.
- Sack RL, Brandes RW, Kendall AR, Lewy AJ. Entrainment of freerunning circadian rhythms by melatonin in blind people. New Engl J Med 2000;343:1070–7.

- Folkard S, Arendt J, Aldhous M, Kennet H. Melatonin stabilises sleep onset time in a blind man without entrainment of cortisol or temperature rhythms. Neurosci Lett 1990;113:193–8.
- Neckelmann D, Mykletun A, Dahl AA. Chronic insomnia as a risk factor for developing anxiety and depression. Sleep 2007;30:873–80.
- Jaussent I, Bouyer J, Ancelin ML, et al. Excessive sleepiness is predictive of cognitive decline in the elderly. Sleep 2012;35:1201–7.
- Edinger JD, Means MK, Carney CE, Krystal AD. Psychomotor performance deficits and their relation to prior nights' sleep among individuals with primary insomnia. Sleep 2008;31:599–607.
- Okawa M, Uchiyama M. Circadian rhythm sleep disorders: characteristics and entrained pathology in delayed sleep phase and non-24 sleep–wake syndrome. Sleep Med Rev 2007;11:485–96.
- Abe T, Inoue Y, Komada Y, et al., Relation between morningness–eveningness score and depressive symptom among patients with delayed sleep phase syndrome. Sleep Med 2011;12:680–4.
- Elliott DB, Hurst MA, Weatherill J. Comparing clinical tests of visual function in cataract with the patient's perceived visual disability. Eye 1990;4:712–7.
- Rubin GS, Bandeen-Roche K, Huang GH, et al. The association of multiple visual impairments with self-reported visual disability: SEE project. Invest Ophthalmol Vis Sci 2001;42:64–72.

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