

The current study has several limitations. First, details on the characteristics of non-participants were not clarified. The data collection rate from the mothers of 2- to 3-year-old children was significantly higher than that from the mothers of 4- to 5-year-old children. The reason for this phenomenon is not clear. However, considering that the number of nursery staff in 2- to 3-year-old children class is more than that in 4- to 5-year-old children class (Japanese law, Child Welfare Act), there might be a closer connection between nursery staff and mothers, possibly contributing to the difference in collection rate. The reason why more mothers of boys agree to participate could not be clarified.

Secondly, although the sleep habits of children are affected by socio-cultural environments, socioeconomic, ethics of the family (Giannotti et al. 2005; Crosby et al. 2005), data on age, income, and educational background of parents were not obtained. Thus, the results should be interpreted with caution. Thirdly, no objective measures were applied to the data either on sleep habits or behavior problems. Furthermore, only 3 items of the CBCL (i.e., attention problems, aggressive behavior, and the anxious/depressed category) were used in this study to estimate behavioral problems. However, as for sleep habits, it has been reported that there were overall similarities between actigraph sleep measures and mother-reported measures (Acebo et al. 2005). As for behavior problems, although the CBCL is widely used and well validated, assessment of behavior problems by other estimators has been recommended (Aronen et al. 2009). Further investigations of other variables about behavioral problems not only by mothers but also by nursery school teachers would be informative.

This study revealed a small but significant association between behavioral problems and poor sleep habits including short sleep duration and irregular bedtime among pre-school-age nursery school children. Our results support the idea that it is necessary for preschool-age nursery school children to sleep regularly and adequately. The mother's work and daily schedule was regarded as a key to the sleep habits of Japanese children. The importance of appropriate limit-setting in cooperation with other family members should be emphasized so that we can protect children's sleep.

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Conflict of Interest

None of the authors have any conflicts of interest associated with this study.

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Insomnia as a Risk for Depression: A Longitudinal Epidemiologic Study on a Japanese Rural Cohort

Isa Okajima, PhD; Yoko Komada, PhD; Takashi Nomura, MD, PhD;
Kenji Nakashima, MD, PhD; and Yuichi Inoue, MD, PhD

ABSTRACT

Objectives: To determine (1) whether insomnia is a factor related to the presence or persistence of depression for 2 years in the Japanese population and (2) which component of insomnia is associated with the presence of depression for 2 years in a rural cohort.

Method: This is a community-based longitudinal study. Two thousand eight hundred twenty-five people aged 20 years or older were evaluated at baseline, and of those participants, 1,577 (56%) were reevaluated after 2 years. During both surveys, the participants were asked to describe demographic variables and to fill out self-rating scales of insomnia (Pittsburgh Sleep Quality Index [PSQI]) and depressive symptoms (Center for Epidemiologic Studies Depression Scale).

Results: The results of a multiple logistic regression analysis showed that depression (OR = 6.0; 95% CI, 4.4–8.0) and insomnia (OR = 2.1; 95% CI, 1.5–2.8) at baseline were significantly associated with the presence of depression at the follow-up. Most of the PSQI subscales, except for sleep duration and habitual sleep efficiency, were significantly associated ($P < .01$) with the presence of depression at the follow-up. In addition, the new appearance and repeated existence of depression at the follow-up were related to persistent insomnia (adjusted ORs = 7.0 and 3.3 [$P < .001$], respectively). A result of the receiver operating characteristic curve showed that persons with insomnia whose PSQI scores exceeded 8 points at the baseline were most likely to still have insomnia at the follow-up (cutoff point = 7.5).

Conclusions: On the basis of our results in a Japanese population, insomnia with high severity level could be a risk factor for the presence/persistence of depression in the long-term prognosis.

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Corresponding author: Yuichi Inoue, MD, PhD,
Department of Somnology, Tokyo Medical University,
6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo 160-0023,
Japan (inoue@somnology.com).

Insomnia is well-known as a common disorder with an extremely high prevalence,^{1–3} and it has been reported that one-fifth of the general population in Japan has symptoms related to insomnia.⁴ In addition, insomnia is suspected to be a risk factor for the development of other psychiatric disorders (eg, anxiety disorders, depressive disorders, and substance abuse),^{5,6} and particularly, its association with depression has been widely accepted.^{7,8}

The results of previous longitudinal epidemiologic studies^{5,7,9} have revealed that people who had suffered from persistent insomnia from the baseline to a follow-up survey conducted several years later had a markedly increased risk for developing depression at the follow-up compared to people who had not suffered from insomnia. This finding was consistent in studies of young adults^{6,10} and of older adults.^{11,12} Therefore, insomnia is considered an important risk factor for the development of depression. However, thus far, no longitudinal study has been performed in Japan regarding this issue. In addition, previous studies have not yet elucidated which of the insomnia symptoms (eg, sleep quality, sleep onset latency, sleep duration, sleep efficiency, and daytime dysfunction) becomes a risk factor for developing depression. Moreover, the relationship between the occurrence and persistence/disappearance of insomnia symptoms in a long-term interval and the development of depression has not been sufficiently confirmed, especially in the Asian population. In addition, if the chronicity of insomnia is actually involved in the development of depressive symptoms, it still remains unclear as to what level of insomnia severity leads to chronic morbidity of insomnia.

In order to clarify these issues, we conducted a longitudinal study on the basis of an anonymous self-rating questionnaire survey over a 2-year interval on a rural population cohort in Japan.

METHOD

Participants and Procedure

The Ethics Committee of Tottori University, Tottori, Japan, approved this study. Two-point epidemiologic surveys with a 2-year interval were performed on the same adult cohort in the town of Daisen in Tottori Prefecture, Japan. In 2004, the total population of the town was 6,643, and there were 5,528 residents aged 20 years or older (2,521 men, 3,007 women, mean age = 55.2 years). The questionnaire survey was conducted from November 2005 to January 2006 as the first survey (baseline) and from November to December 2007 as the second survey (follow-up). With the cooperation of local public health nurses, questionnaires with individual code numbers were delivered to all residents aged 20 years and older at baseline and at follow-up. All the participants gave their written informed consent to participate in this study at the time of questionnaire delivery. Response to the questionnaire was obtained from 2,825 people anonymously at the baseline survey (responder rate, 51%; 1,220 men, 1,605 women; mean [SD] age = 57.4 [17.7] years). Two years later, a follow-up survey was conducted of the people who had submitted responses for the baseline survey, and 1,577 of them responded to the questionnaire (responder rate, 56%; 683 men, 894 women; mean [SD] age = 58.6 [16.1] years; Figure 1). The respondents of the 2 surveys were matched using code numbers.

- Patients with chronic insomnia are highly likely to develop and sustain depression.
- Current evidence best supports the position that early intervention for insomnia patients with 7.5 or higher score on the Pittsburgh Sleep Quality Index can be helpful for the prevention, onset, and relapse of depression.

Measures

The contents of the questionnaire were as follows:

(1) Demographic variables—The participants were asked about their age, gender, disease currently treated (“What kind of disease you are currently being treated for?”), family constitution (“Do you currently live with your family?”), smoking habits (“Do you currently smoke?”), and alcohol habits (“Do you currently have a drinking habit?”).

(2) The Japanese version of the Pittsburgh Sleep Quality Index (PSQI)¹³—We used the scale for estimating sleep disturbance. The PSQI included subitems evaluating sleep quality (C1), sleep latency (C2), sleep duration (C3), habitual sleep efficiency (C4), sleep disturbance (C5), use of sleeping medication (C6), and daytime dysfunction (C7). The cutoff score of PSQI for insomnia was already determined to be 5.5 points.¹³ Therefore, in this study, responders with PSQI scores of 6 or higher were considered to have insomnia.

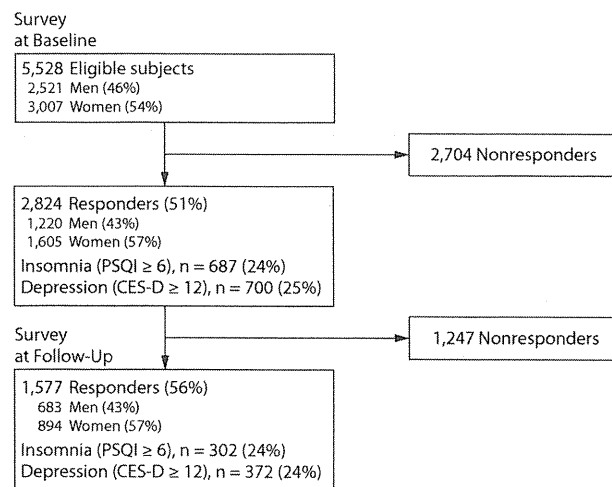
(3) Twelve-item version of the Center for Epidemiologic Studies Depression Scale (CES-D)¹⁴—We used the scale for estimating depressive symptoms similar to the report by Kaneita et al.¹⁵ The scale had 4 response options, namely, “never or rarely,” “sometimes,” “often,” and “always,” which were coded 0 to 3, respectively. We used the total scores of CES-D as parameters of depression, and the scores were divided into 3 categories: 0 to 11 as normal, 12 to 20 as moderate, and 21 to 36 as severe.¹⁴ On the basis of these criteria, we classified the participants into a nondepression group (CES-D score <12) and a depression group (CES-D score ≥12).

Statistical Analysis

All statistical and receiver operating characteristic (ROC) analyses were performed using SPSS (version 11.5, SPSS Japan, Inc, Tokyo) unless otherwise stated.

Using the above-mentioned standard cutoff score of PSQI and CES-D, we classified the participants on the basis of the presence/absence of insomnia and depression in both surveys. Using this classification, we performed a univariate and multivariate logistic regression analysis with the presence/absence of depression during the follow-up as a dependent variable and the above-mentioned demographic variables (gender, age, disease currently treated, drinking habit, smoking habit, and living alone) and the presence/absence of insomnia and depression as independent variables. In addition, to determine the insomnia symptom

Figure 1. Participants Flowchart



Abbreviations: CES-D = Center for Epidemiologic Studies Depression Scale, PSQI = Pittsburgh Sleep Quality Index.

component associated with the presence of depression at the follow-up, we conducted univariate and multivariate logistic regression analyses with the presence/absence of depression at the follow-up as a dependent variable and the scores of PSQI subscales as independent variables.

On the basis of the results of the 2 surveys, the participants were divided into 4 insomnia subcategories (ie, i-category 1, the category without insomnia symptoms during both surveys; i-category 2, the category in which participants did not have insomnia symptoms at the baseline but had them at the follow-up; i-category 3, the category in which the participants had insomnia symptoms at the baseline but did not have the symptoms at the follow-up; and i-category 4, the category with insomnia symptoms during both surveys). The participants were also divided into 4 depression subcategories (ie, d-category 1, the category without depressive symptoms at both surveys; d-category 2, the category in which participants did not have depressive symptoms at the baseline but had them at the follow-up; d-category 3, the category in which participants had depressive symptoms at the baseline but did not have them at the follow-up; and d-category 4, the category with depressive symptoms during both surveys). In order to elucidate the association between the changes in the status of insomnia and depression symptoms on the basis of these classifications, we conducted a logistic regression analysis controlling for demographic variables by using the “new appearance of depression at the follow-up” (d-category 1 vs d-category 2) and the “repeated existence of depressive symptoms” (d-category 3 vs d-category 4) as dependent variables and the course patterns of insomnia (i-categories 1, 2, 3, 4) as an independent variable.

Receiver operating characteristic curves¹⁶ were plotted and the mean (95% confidence interval) estimated area under the curve (AUC) for the PSQI score at the baseline was calculated targeting the repeated existence of insomnia at the follow-up. When the slope of the tangent line of the

Table 1. Descriptive Statistics of Demographic Data, the Scores on CES-D and PSQI, and Frequency of Medication Use Among the Participants

Characteristic	Insomnia Negative at Baseline (n = 879)		Insomnia Positive at Baseline (n = 299)	
	Insomnia Negative at Follow-Up (i-category 1, n = 762) ^a	Insomnia Positive at Follow-Up (i-category 2, n = 117) ^b	Insomnia Negative at Follow-Up (i-category 3, n = 128) ^c	Insomnia Positive at Follow-Up (i-category 4, n = 171) ^d
Gender, n				
Male	357	47	52	72
Female	405	70	76	99
Age, mean (SD), y	58.6 (15.8)	60.3 (16.2)	58.1 (15.8)	62.5 (15.9)
Disease currently treated, n (%)				
Baseline	273 (23.2)	41 (3.5)	49 (4.2)	80 (6.8)
Follow-up	295 (25.0)	56 (4.8)	43 (43.7)	94 (8.0)
Drinking habit, n (%)				
Baseline	300 (25.6)	48 (4.1)	50 (4.3)	55 (4.7)
Follow-up	218 (18.6)	41 (3.5)	39 (3.3)	37 (3.1)
Smoking habit, n (%)				
Baseline	143 (12.2)	24 (2.0)	26 (2.2)	31 (2.6)
Follow-up	131 (11.1)	22 (1.9)	25 (2.1)	32 (2.7)
Living alone, n (%)				
Baseline	23 (2.0)	2 (0.2)	4 (0.3)	9 (0.8)
Follow-up	25 (2.2)	4 (0.3)	5 (0.4)	9 (0.8)
CES-D score, mean (SD)				
Baseline	7.1 (4.0)	9.1 (4.4)	10.5 (5.1)	11.9 (5.1)
Follow-up	7.3 (4.0)	11.5 (4.3)	8.9 (3.9)	12.4 (5.1)
PSQI score, mean (SD)				
Baseline	2.7 (1.4)	3.6 (1.3)	7.1 (1.4)	8.4 (2.3)
Follow-up	2.8 (1.4)	7.3 (1.5)	3.6 (1.2)	8.2 (2.3)
Sleeping medication use score, mean (SD) ^e				
Baseline	0.0 (0.1)	0.0 (0.3)	0.4 (1.0)	1.0 (1.3)
Follow-up	0.0 (0.2)	0.7 (1.2)	0.1 (0.4)	1.0 (1.3)

^aIncludes subjects without insomnia symptoms at both surveys.

^bIncludes subjects who did not have insomnia symptoms at the baseline but had symptoms at the follow-up.

^cIncludes subjects who had insomnia symptoms at baseline but did not have symptoms at the follow-up.

^dIncludes subjects with insomnia symptom at both surveys.

^eFrequency of medication use was rated on C6 on PSQI (0, not during the past month; 1, less than once a week; 2, once or twice a week; 3, 3 or more times a week).

Abbreviations: CES-D = Center for Epidemiologic Studies Depression Scale, PSQI = Pittsburgh Sleep Quality Index.

ROC curve was statistically equal to 1 (ie, AUC = 0.5), computed by the SPSS software, the ROC curve was regarded as inaccurate for prediction. The best cutoff value for the repeated existence of insomnia was determined on the basis of sensitivity, specificity, and positive likelihood ratio and negative likelihood ratio. In accordance with the authorized method, the cutoff score was assessed as adequate when positive likelihood ratio was 2.0 or higher and negative likelihood ratio was 0.5 or less.¹⁷

RESULTS

When the demographic data pertaining to the responders who answered only at the baseline (n = 1,247) and those who responded at both the baseline and the follow-up (n = 1,577) were compared, the result showed a significant difference in age ($t_{2394} = -3.56$, $P < .01$; mean [SD] age = 55.9 [19.6] vs 58.6 [16.1] years), but the difference between the 2 groups was only 2.7 years. No gender difference was found. Of the 687 responders who were assessed as having insomnia at baseline, 385 (56.0%) responded at the follow-up. A comparison between the responders who answered only at the baseline and those who responded at both the baseline and the follow-up showed a statistical difference in age ($t_{471} = -2.20$, $P = .02$; mean [SD] age = 56.9 [19.5] vs 60.1 [16.0] years), but

the difference between the 2 groups was only 3.2 years. No gender difference was found (men/women, n/n = 113/143 vs n/n = 154/231; $\chi^2_1 = 1.09$; $P = .3$). The comparison of the percentages of participants with insomnia or depression at each survey showed that the percentages were almost similar in both surveys ([insomnia] baseline, 24.0%; follow-up, 24.3%; [depression] baseline, 24.9%; follow-up, 24.4%). The participants who belonged to i-category 1 accounted for 64.2%; i-category 2, 9.9%; i-category 3, 10.9%; and i-category 4, 14.5%. Table 1 shows the demographic data of each survey, the CES-D scores, PSQI total scores, and frequency of the use of sleep medication manifested as C6 score of the PSQI scale. The number of participants taking sleep medication 3 days a week or more (C6 score = 3) was 82 (5.6%) at baseline and 105 (7.0%) at follow-up. A total of 161 participants (10.6%) answered that they had received treatment for insomnia in the period between the 2 surveys.

Association Between the Baseline Data and the Presence/Absence of Depression at the Follow-Up

To examine the risk factors on the presence of depression at the follow-up, we conducted univariate and multivariate logistic regression analyses. The results of both analyses revealed that CES-D score ≥ 12 and PSQI score ≥ 6 at the

Table 2. Logistic Regression Analysis on the Associated Factors for the Existence of Depression (CES-D score ≥ 12) at the Follow-Up Among the Descriptive Variables^a

Baseline	Total Sample, N	Positive for Depression at the Follow-Up, n (%)	Univariate Relative Risk (95% CI) ^b	P	Multivariate Relative Risk (95% CI)	P
Gender						
Male	664	148 (22.3)				
Female	871	224 (25.7)		NS		NS
Age^c						
< 60	666	169 (25.4)				
≥ 60	868	203 (23.4)		NS		NS
Disease currently treated						
No	933	218 (23.4)				
Yes	602	154 (25.6)		NS		NS
Drinking habit						
No	955	225 (23.6)				
Yes	563	243 (43.2)		NS		NS
Smoking habit						
No	1,247	288 (23.1)				
Yes	272	79 (29.0)	1.4 (1.0–1.8)	.04		NS
Living alone						
No	1,493	348 (24.0)				
Yes	66	22 (34.4)		NS		NS
CES-D score						
< 12	1,131	168 (14.9)				
≥ 12	320	180 (56.3)	7.4 (5.6–9.7)	<.001	6.0 (4.4–8.0)	<.001
PSQI score						
< 6	1,052	188 (17.9)				
≥ 6	376	160 (42.6)	3.4 (2.6–4.4)	<.001	2.1 (1.5–2.8)	<.001

^aThe analyses within this table were conducted on the subset with complete data for each variable.

^bRelative risks approximated with odds ratios.

^cThe age category was divided at the median age (= 60 years old).

Abbreviations: CES-D = Center for Epidemiologic Studies Depression Scale, NS = nonsignificant, PSQI = Pittsburgh Sleep Quality Index.

Table 3. Logistic Regression Analysis on the Associated Factor for the Existence of Depression (CES-D score ≥ 12) at the Follow-Up Among PSQI Variables

PSQI Subitem	Univariate Relative Risk (95% CI) ^a	P	Multivariate Relative Risk (95% CI)	P
C1: sleep quality	2.6 (2.1–3.2)	<.01	1.6 (1.3–2.1)	<.01
C2: sleep latency	1.7 (1.5–2.0)	<.01	1.2 (1.0–1.5)	<.01
C3: sleep duration	1.1 (1.0–1.3)	NS	1.1 (0.9–1.3)	NS
C4: habitual sleep efficiency	1.5 (1.3–1.8)	<.01	1.1 (0.9–1.3)	NS
C5: sleep disturbance	2.5 (2.0–3.1)	<.01	1.3 (1.0–1.7)	<.01
C6: use of sleeping medication	1.5 (1.3–1.8)	<.01	1.2 (1.0–1.4)	<.01
C7: daytime dysfunction	2.3 (1.9–2.8)	<.01	1.8 (1.4–2.2)	<.01

^aRelative risks approximated with odds ratios.

Abbreviations: CES-D = Center for Epidemiologic Studies Depression Scale, NS = nonsignificant, PSQI = Pittsburgh Sleep Quality Index.

baseline were factors significantly associated with the presence of depression at the follow-up ([CES-D] univariate OR = 7.4; 95% CI, 5.6–9.7; multivariate OR = 6.0; 95% CI, 4.4–8.0; [PSQI] univariate OR = 3.4; 95% CI, 2.6–4.4; multivariate OR = 2.1; 95% CI, 1.5–2.8; respectively [Table 2]). The same result was obtained from the multivariate logistic regression analysis when the item for insomnia was excluded from the total CES-D score and item C7, which may assess depressive thought, was excluded from the total PSQI ([CES-D] OR = 4.5; 95% CI, 3.3–6.2; [PSQI] OR = 1.6; 95% CI, 1.1–2.2).

Since it was revealed that the existence of insomnia at baseline was associated with the presence of depressive symptoms at follow-up, we conducted univariate and multivariate logistic regression analyses to examine which of the insomnia symptom components were associated with

depression at the follow-up. The results showed that poor quality of sleep (C1, OR = 1.6), sleep latency (C2, OR = 1.2), sleep disturbance (C5, OR = 1.3), use of sleeping medication (C6, OR = 1.2), and daytime dysfunction (C7, OR = 1.8) at the baseline were factors significantly related to the presence of depression at the follow-up (Table 3). However, sleep duration (C3) and habitual sleep efficiency (C4) did not appear to be significantly associated factors.

Examining the Association Between Symptoms of Insomnia and Depression Through the 2 Surveys

The results of the logistic regression analysis showed that i-category 2 (OR = 10.0) and i-category 4 (OR = 7.0) were significantly associated factors for the new appearance of depression at the follow-up in comparison to i-category 1. In addition, it was revealed that i-category 4 (OR = 3.3) was

Table 4. Associated Risk for the New Appearance of Depression at Follow-Up or the Repeated Existence of the Symptom at 2 Surveys in Relation to the Variations of Insomnia Course Pattern Categories^a

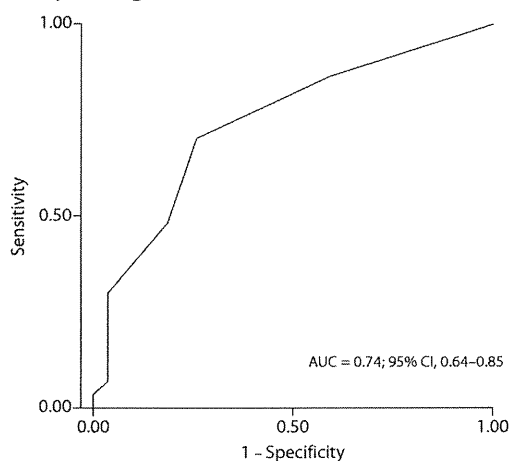
Variable	i-Category 1 (n = 762)	i-Category 2 (n = 117)	i-Category 3 (n = 128)	i-Category 4 (n = 171)
New appearance of depressive symptom at follow-up, n (%)	48 (6.3)	39 (33.3)	10 (7.8)	29 (17.0)
Unadjusted odds ratio (95% CI)	...	10.1 (6.0–16.8)*	1.8 (0.9–3.7)	6.3 (3.6–10.9)*
Adjusted odds ratio (95% CI) ^b	...	10.0 (5.9–16.7)*	1.8 (0.9–3.7)	7.0 (3.9–12.2)*
Repeated existence of depressive symptom, n (%)	40 (5.3)	16 (13.7)	16 (12.5)	54 (31.6)
Unadjusted odds ratio (95% CI)	...	2.3 (1.0–5.9)	0.7 (0.4–1.6)	2.8 (1.5–5.4)*
Adjusted odds ratio (95% CI) ^b	...	2.5 (0.9–6.8)	0.7 (0.3–1.6)	3.3 (1.6–6.6)*

^ai-Category 1: the category of subjects without insomnia symptoms at both surveys; i-category 2: the category in which subjects did not have insomnia symptoms at the baseline but had symptoms at the follow-up; i-category 3: the category in which subjects had insomnia symptoms at baseline but did not have symptoms at the follow-up; i-category 4: the category of subjects with insomnia symptoms at both surveys.

^bOdds ratio adjusted for the factors including gender, age, disease currently treated, habitual alcohol ingestion, smoking habit, and living alone, with i-category 1 as the reference.

**P* < .001.

Figure 2. Cutoff Point of the Pittsburgh Sleep Quality Index for the Repeated Existence of Insomnia Estimated With Receiver Operating Characteristic Curve



Cutoff Point	Sensitivity	Specificity	Positive Likelihood Ratio	Negative Likelihood Ratio
5.0	1.00	0.00	1.00	...
6.5	0.86	0.41	1.45	0.34
7.5	0.70	0.74	2.70	0.40
8.5	0.48	0.81	2.61	0.63

Abbreviation: AUC = area under the curve.

a factor significantly associated with the repeated existence of depression (Table 4).

The PSQI Cutoff Score for Predicting the Existence of Depression at the Follow-Up

The results described above revealed that the repeated existence of insomnia (i-category 4) has an influence on both the new appearance of depression and the repeated existence of depression at the follow-up. Therefore, we used the ROC curve to examine the cutoff value of the PSQI scores at the baseline for participants who repeatedly had insomnia at the follow-up. As a result, AUC of the ROC curve was 0.74 (95% CI, 0.64–0.85), and it was statistically larger than 0.50. The cutoff value of the PSQI at baseline was estimated at 7.5 points. This cutoff value’s sensitivity was 70%, specificity was 74%, positive likelihood ratio was 2.70, and negative likelihood ratio was 0.40 (Figure 2).

DISCUSSION

We conducted a longitudinal study over a 2-year interval on a rural population cohort in Japan to examine whether persistent insomnia was a risk factor for the existence of depression at the follow-up using a multivariate logistic regression analysis. The results revealed that the risk of depression at the follow-up was high, with an OR of 2.1 for people with insomnia at the baseline. This finding is compatible with the reports in Western countries.^{5,7} In addition, OR values between 2 and 4 reported in previous cohort studies for the later existence of depression relating to the presence of insomnia at the baseline^{7,12,18} were equivalent to the results of this study (OR = 2.1).

This is the first study examining the relationship between each insomnia symptom component at the baseline and the presence of depression at the follow-up from a prognostic viewpoint. As a result, poor quality of sleep (C1), sleep latency (C2), sleep disturbance (C5), use of sleeping medication (C6), and daytime dysfunction (C7) were significantly associated with the presence of depression at follow-up. Few studies have examined the symptom components of insomnia associated with depression. In the report by Chang et al,¹⁹ people’s poor quality of sleep and less than 7 hours of sleep during their university days were associated with the occurrence of depression in the later years. Because their study showed the association between insomnia and depression occurring 30 or more years later, a simple comparison with our study results is not possible, although the findings of our study and those of Chang’s study¹⁹ are congruent with respect to the fact that poor quality of sleep was involved in the risk factors of later occurrence of depression. Early morning awakening has been believed to be a pathognomonic symptom of depression.²⁰ Recently, however, cross-sectional surveys^{15,21} have shown that difficulty in initiating sleep is a factor associated with the presence of depressive symptoms. In particular, a study by Kaneita et al¹⁵ conducted on a community sample of persons aged 20 years or older in a cross-sectional survey revealed that, among the symptoms of insomnia, difficulty in initiating sleep had the highest odds of association with depression (difficulty initiating sleep,

OR = 1.56; difficulty maintaining sleep, OR = 1.49; early morning awakening, OR = 1.34). Interestingly, our result showed that difficulty in initiating sleep at the baseline was indicated as a possible long-term risk factor for the presence (development or persistence) of depression. In other words, from the prophylactic viewpoint, clinicians treating patients who complain of difficulty in initiating sleep should consider the possibility of future development of depression.

The results of the relationship between the successive changes in the status of both insomnia and depression have shown that the new appearance and the repeated existence of insomnia are significantly associated with the new appearance of depression during the follow-up, and that the repeated existence of insomnia is significantly associated with the repeated existence of depression in both surveys. Previous studies have shown that the existence of insomnia that persisted for 2 weeks or more sometime during the survey period was significantly predictive of developing a major depressive episode.¹⁰ In addition, it has been reported that, in people who were affected with persistent insomnia for 1 year, the risk of developing depression 1 year later was high, with an OR in a subsequent survey of about 40.⁹ The results of this study showed that for people whose insomnia lasted for 2 years, the ORs of a new appearance of depression at the follow-up and of the repeated existence of depression were 7 and 3, respectively. These findings indicate that persistent insomnia is strongly related to the development and prolongation of depression, although there was a difference in the odds ratio between the studies, possibly because of a difference in terms of target populations and survey methods. Therefore, from the perspective of the prevention of depression, it would be clearly important to prevent chronicity and development of insomnia.

It is noteworthy that the results of the ROC curve revealed that, in the 2-year prognosis, insomnia was highly likely to appear repeatedly in people whose PSQI score exceeded 8 points at the baseline. The PSQI cutoff score for the chronicity of insomnia in the participants examined in this study (7.5 points) was unexpectedly lower than the general average PSQI score of patients with chronic insomnia examined in a clinical setting (range of mean scores: 10–12 points).^{22,23} However, undoubtedly, the patients in clinical settings who seek treatment for insomnia experience a higher severity of the symptom than the general population. In addition, while the majority of patients with chronic insomnia in a clinical setting use sleep medication,²⁴ the frequency of the use of sleep medication by the participants examined in this study was extremely low (baseline C6 mean score, 0.23; the number of participants who used medication for 3 days a week or more, 89 [5.6%]; follow-up C6 mean score, 0.27; the number of participants who used medication for 3 days a week or more, 105 [7.0%]), and this might have played a role in the low score of PSQI in the participants with insomnia in our study. Thus, in order to prevent the subsequent development of depression, intensive treatment would presumably be necessary for the cases with PSQI scores of 8 or above if they do not take any sleep medication.

Limitations

First, we used the cutoff value of an established questionnaire-based rating scale to define insomnia and depression in this study. To obtain an accurate diagnosis, it might be necessary to diagnose through structured interviews. The findings of our study, which showed that insomnia at the baseline is a factor related to the long-term development of depression, are relatively consistent with previous studies in which participants were diagnosed using a structured interview.^{7,10} Therefore, the results of this study regarding this issue are unlikely to deviate much from the actual conditions.

Second, the 12-item version of CES-D we used includes an item inquiring the severity of insomnia, and item C7 of PSQI may assess depressive thought (the problem of keeping up enough enthusiasm to get things done). However, we confirmed that the same results were obtained after excluding these items from the CES-D and the PSQI.

Third, we classified the successive changes in the status of insomnia and depression into 4 categories on the basis of survey scores obtained at 2 points in time, but because the 2 surveys were separated by a long interval of 2 years, the changes in insomnia and depressive symptoms may not have been assessed accurately. Therefore, it is unclear whether insomnia actually precedes or follows the occurrence of depression in the participants. In other words, our categorization does not apply to the cases wherein symptom levels have changed several times during the survey period, and this point cannot be elucidated through this study. To clarify this issue, future studies should use more frequent assessments with monthly or longer reference periods to obtain more reliable data about insomnia, as indicated by Morin et al.²⁵

Finally, the response rate was approximately 50% at both survey points in this study. However, a sampling bias was considered to be relatively small, because a significant but small difference was observed only in age when demographic variables of the responders who answered only at the baseline and of those who responded to both the surveys were compared.

CONCLUSION

Our results revealed that insomnia is a risk factor for the development and persistence of depression in Japan, and insomnia symptoms, especially poor quality of sleep, difficulty in initiating sleep, and daytime dysfunction, are factors significantly related to depression. In addition, the results suggested that persistent insomnia is likely to increase the risk of new appearance or repeated existence of depression in the long-term prognosis. In particular, insomnia is highly likely to become chronic in people with untreated insomnia with PSQI scores of 8 or higher, and this outcome may lead to the risk of development and persistence of depression. These results emphasize that insomnia needs to be treated cautiously to prevent the occurrence of depression.

Author affiliations: Japan Somnology Center, Neuropsychiatric Research Institute, Tokyo (Drs Okajima and Inoue); Department of Somnology, Tokyo Medical University (Drs Okajima, Komada, and Inoue); and Department of Neurology, Institute of the Neurological Sciences, Tottori University Faculty of Medicine, Tottori (Drs Nomura and Nakashima), Japan.

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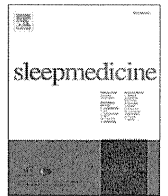
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Original Article

Quality of life in patients with narcolepsy with cataplexy, narcolepsy without cataplexy, and idiopathic hypersomnia without long sleep time: Comparison between patients on psychostimulants, drug-naïve patients and the general Japanese population

Akiko Ozaki^{a,b}, Yuichi Inoue^{b,c,*}, Kenichi Hayashida^b, Toru Nakajima^{b,d}, Makoto Honda^{b,e}, Akira Usui^{b,f}, Yoko Komada^{b,c}, Mina Kobayashi^b, Kiyohisa Takahashi^{b,g}

^aSchool of Nursing, Faculty of Nursing, Toho University, Tokyo, Japan

^bJapan Somnology Centre, Neuropsychiatric Research Institute, Tokyo, Japan

^cDepartment of Psychiatry, Tokyo Medical University, Tokyo, Japan

^dDepartment of Neuropsychiatry, School of Medicine, Kyorin University, Tokyo, Japan

^eSleep Disorder Research Project, Tokyo Institute of Psychiatry, Tokyo, Japan

^fFaculty of Health Science Technology, Bunkyo Gakuin University, Tokyo, Japan

^gJapan Foundation for Neuroscience and Mental Health, Tokyo, Japan

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ABSTRACT

Objective: To assess the quality of life of patients with narcolepsy with cataplexy (NA-CA), narcolepsy without cataplexy (NA w/o CA), and idiopathic hypersomnia without long sleep time (IHS w/o LST) who were taking psychostimulant medication, and to ascertain which factors (including psychosocial and environmental variables) influence quality of life in this population.

Methods: In total, 185 patients who had received regular treatment were enrolled in the study (NA-CA, $n = 83$; NA w/o CA, $n = 48$; IHS w/o LST, $n = 54$). Patients were asked to complete questionnaires including the Short Form-36 Health Survey (SF-36), the Epworth Sleepiness Scale (ESS), and items concerning psychosocial and environmental variables.

Results: All three diagnostic groups had significantly lower scores for most SF-36 domains compared with the Japanese normative data, and the ESS score was significantly reduced with treatment. Multiple logistic regression analyses revealed that several SF-36 domains were associated with the ESS score; autonomy in controlling own job schedule, experience of divorce or break up with a partner due to symptoms, experience of being forced to relocate or being dismissed due to symptoms, and perception of support from others.

Conclusions: The severity of subjective sleepiness and psychological and environmental variables influenced quality of life in patients with these hypersomnias of central origin.

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1. Introduction

Excessive daytime sleepiness (EDS), including hypersomnias of central origin, affects 9–17% of the general population [1–4]. Narcolepsy is quite rare, with a prevalence of approximately 0.02–0.05% in Western countries [5–7]. The highest reported prevalence is 0.16%, and this was reported in a Japanese population [8]. However, narcolepsy has clear impacts on the functions of daily life. Several previous studies have demonstrated relationships between

hypersomnias of central origin (especially narcolepsy), severe limitations and difficulties in everyday life activities (including school, work, interpersonal relationships, and social activities) [9,10], and decreased quality of life (QOL) [11–16]. It has been recently reported that drug-naïve patients suffering from narcolepsy with cataplexy (NA-CA), narcolepsy without cataplexy (NA w/o CA), and idiopathic hypersomnia without long sleep time (IHS w/o LST) have poorer QOL compared with the general population, and that the severity of subjective sleepiness is not related to the degree of decline of QOL among these patients [17].

Treatment with psychostimulant medication has been widely accepted as the first-line treatment for patients with the above-mentioned hypersomnias. Some studies have shown that treatment with psychostimulant medication improves both EDS and

* Corresponding author at: Japan Somnology Centre, Neuropsychiatric Research Institute, 1-24-10 Yoyogi, Shibuya-ku, Tokyo 151-0053, Japan. Tel.: +81 3 3374 9112; fax: +81 3 3374 9125.

E-mail address: inoue@somnology.com (Y. Inoue).

QOL [15,18]. However, it has not been determined whether treatment with psychostimulant medication improves QOL to a normal level in patients with hypersomnia. As QOL is a comprehensive and multidimensional concept, it can reflect not only health status but also psychological, social, and environmental variables of an individual's life, including lifestyle and social support. Therefore, such variables should be taken into consideration when evaluating QOL. However, to the authors' knowledge, no studies have considered environmental variables when investigating the association between hypersomnia and QOL in treated patients with hypersomnia of central origin.

The aims of this cross-sectional study were: (1) to assess QOL among treated patients with NA-CA, NA w/o CA, and IHS w/o LST compared with drug-naïve patients [17] and Japanese normative data; and (2) to investigate the impact of psychostimulant medication and psychosocial and environmental variables on QOL.

2. Methods

The present study was approved by the Ethics Committee of the Neuropsychiatric Research Institute. Informed consent was obtained from all participants.

2.1. Participants

Among consecutive eligible patients (aged ≥ 20 years) who visited the outpatient clinic of the Japanese Somnology Centre between May 2007 and March 2009, patients who met the following two inclusion criteria were enrolled in this study: (1) a diagnosis of NA-CA, NA w/o CA, or IHS w/o LST based on the diagnostic criteria in the Second Edition of the International Classification of Sleep Disorders [19]; and (2) regular treatment with psychostimulant medication for EDS with more than one year of follow-up after fixation of the dose [mean duration of treatment 35.4 ± 20.3 months]. Moreover, patients with any of the following four conditions were excluded: (1) apnoea-hypopnoea index $> 5/h$ and/or periodic limb movement index $> 15/h$ on nocturnal polysomnography (PSG); (2) possible circadian rhythm sleep disorders or behaviourally induced insufficient sleep syndrome judged from sleep diaries; (3) possible comorbidities of psychiatric disorders (including mood disorders and other major medical illnesses); and (4) habitually taking drugs or substances with psychotropic effects. Before starting treatment, diagnoses were made for all participants according to the above criteria by at least two board-certified psychiatrists specializing in sleep disorders.

Consequently, 183 patients (83 patients with NA-CA, 48 patients with NA w/o CA, and 54 patients with IHS w/o LST) were enrolled in the study. All subjects with NA w/o CA or IHS w/o LST underwent overnight PSG followed by a standard multiple sleep latency test (MSLT) [20] for diagnosis of the disorders. Of the 83 NA-CA subjects, 50 did not undergo MSLT but had both typical cataplexy and a sleep-onset rapid eye movement period (SOREMP) on overnight PSG. The remaining patients with NA-CA and those with NA w/o CA had at least two SOREMPs and less than 8 min of mean sleep latency on MSLT. Patients with IHS w/o LST had less than 8 min of mean sleep latency and one SOREMP or less on MSLT. Due to an insufficient number of patients, patients with IHS with LST ($n = 5$) were not included in this study.

For comparison, 137 newly diagnosed and drug-naïve patients with NA-CA ($n = 28$), NA w/o CA ($n = 27$), and IHS w/o LST ($n = 82$) who had participated in a previous study [17] were included for analysis in the present study. Thirteen of these patients (7%) also participated in the present study.

2.2. Measures

The participants were asked to complete a questionnaire that included an instrument assessing QOL, an instrument evaluating subjective sleepiness, and questions regarding sociodemographic and psychosocial variables. Additional clinical information including demographic variables was also obtained from the participants' medical records.

2.2.1. Medical outcomes study Short Form-36

QOL was assessed using the Japanese version of the Short Form-36 Health Survey questionnaire (SF-36, Version 1.2), a self-administered questionnaire that has been widely used and validated in the general Japanese population [21–23]. The questionnaire consists of 36 questions divided into eight domains that represent different aspects of QOL: (1) physical functioning (PF), (2) role limitations due to physical problems (RP), (3) role limitations due to emotional problems (RE), (4) social functioning (SF), (5) mental health (MH), (6) energy/vitality (VT), (7) bodily pain (BP), and (8) general health (GH).

2.2.2. Epworth Sleepiness Scale

Subjective sleepiness was assessed at the first visit to the outpatient clinic and at the time of the survey using the Epworth Sleepiness Scale (ESS) [24]. The ESS is a widely accepted self-completion questionnaire designed to evaluate the level of sleepiness during daily life. Participants were asked to score the possibility of falling asleep in eight different situations (0 = would never doze; 3 = high chance of dozing, final score range 0–24) [24].

2.2.3. Clinical information and sociodemographic variables

Clinical information obtained included age, gender, age at onset of hypersomnia, length of subjective hypersomnia morbidity, and prescribed medications for the treatment of hypersomnia or cataplexy. Furthermore, questionnaires regarding sociodemographic and psychosocial variables were designed specifically for the present study. Sociodemographic variables included marital status, number of family members in the household, and occupation. The questionnaires also inquired whether hypersomnia had caused problems in different aspects of life, such as relationships and work. Questions about the experience of divorce or a break up with a partner due to symptoms, and the experience of being forced to relocate or being dismissed due to symptoms, were included. In addition, specific questions about autonomous control of job schedule, including the ability to take naps, and questions about perceived support from family, friends, superiors, or coworkers were embedded [25,26].

2.3. Statistical analysis

First, demographic, sociodemographic and clinical variables were compared between the treated patients and the drug-naïve patients. The *t*-test was used to compare continuous variables, and the Chi-squared test was used to compare categorical variables.

Furthermore, demographic, sociodemographic, and clinical variables were compared between the treated patients in the three diagnostic groups (NA-CA, NA w/o CA, and IHS w/o LST). One-way analysis of variance (ANOVA), followed by post-hoc analysis using Scheffe's test, was used to compare continuous variables, and Chi-squared test was used to compare categorical variables. Moreover, in order to assess treatment effectiveness among the treated patients, the paired *t*-test was used to compare ESS scores between pre- and post-treatment periods.

The scores for the eight subscales of the SF-36 were converted into a Japanese norm-based score according to gender and age (standardized *t* score transformation with a mean of 50 ± 10)

Table 1
Descriptive variables of treated patients and drug-naïve patients.

Characteristics	Treated patients				Comparison between three diagnostic groups of treated patients	Drug-naïve patients ^a				Comparison between treated patients and drug-naïve patients
	Overall	NA–CA	NA w/o CA	IHS w/o LST		Overall	NA–CA	NA w/o CA	IHS w/o LST	
Number of participants	185	83	48	54		137	28	27	82	
Gender (%)										
Male	55.1	51.8	52.1	63.0	n.s.	48.2	35.7	37.0	56.1	n.s.
Female	44.9	48.2	47.9	37.0		51.8	64.3	63.0	49.3	
Age (years)										
Mean (SD)	32.6 ± 8.3	33.2 ± 9.8	30.5 ± 6.0	33.3 ± 7.0	n.s.	31.2 ± 9.2	33.2 ± 13.0	28.6 ± 8.6	31.4 ± 7.6	n.s.
Age at onset (years)										
Mean (SD)	17.9 ± 7.1	17.9 ± 8.2	16.0 ± 4.9	19.5 ± 6.7 ^b	0.044	18.6 ± 6.7	18.8 ± 7.0	17.8 ± 4.2	18.8 ± 7.2	n.s.
Duration of disease morbidity (years)										
Mean (SD)	14.6 ± 7.7	15.0 ± 7.7	14.6 ± 7.0	14.0 ± 8.3	n.s.	12.6 ± 8.5	14.4 ± 12.3	11.0 ± 8.7	12.5 ± 6.6	0.021
Marital status (%)										
Married	20.0	21.3	13.6	23.5	n.s.	26.3	17.9	11.1	34.1	n.s.
Not married	80.0	78.7	86.4	76.5		73.7	82.1	88.9	65.9	
Number of family members (%)										
≥ 1	56.2	62.7	47.9	53.7	n.s.	60.6	75.0	40.7	62.2	n.s.
0		33.5	24.1	43.8	38.9		32.8	21.4	48.1	31.7
Missing	10.3	13.3	8.3	7.4		6.6	3.6	11.1	6.1	
Occupation (%)										
Employed (full time)	72.4	59.0	83.3	83.3	0.017	64.7	60.7	55.6	68.3	n.s.
Employed (part time)	11.9	16.9	8.3	7.4		11.0	14.3	22.2	6.1	
Housewife	2.7	4.8	0	1.9		7.4	10.7	7.4	6.1	
Student	10.9	16.8	4.2	7.4		15.4	14.3	11.1	17.1	
Missing	2.2	2.4	4.2	0		1.5	0	3.7	2.4	
ESS score (before treatment)										
Mean (SD)	16.0 ± 4.0	16.6 ± 3.6	16.5 ± 4.2	14.7 ± 4.2 ^c	0.021	14.8 ± 3.3	16.9 ± 2.8	14.5 ± 2.7 ⁱ	14.1 ± 3.3 ^j	n.s.
ESS score (after treatment)										
Mean (SD)	12.8 ± 5.1 ^d	14.1 ± 4.7 ^e	12.8 ± 5.7 ^f	11.0 ± 4.6 ^{g,h}	0.002					
Medication type (%)										
Stimulant and anticataplexy	9.7	21.7	0	0	<0.001					
Stimulant only	90.3	78.3	100.0	100.0						
Stimulant medication type (%)										
Modafinil only	17.8	15.7	18.8	20.4	n.s.					
Methylphenidate only	17.3	18.1	25.0	9.3						
Pemoline only	29.7	24.1	27.1	40.7						
Two medications or more	35.1	42.2	29.2	29.6						

NA–CA, narcolepsy with cataplexy; NA w/o CA, narcolepsy without cataplexy; IHS w/o LST, idiopathic hypersomnia without long sleep time; ESS, Epworth Sleepiness Scale; n.s., not significant; SD, standard deviation.

^a Data from the authors' previous research (2008).

^b Vs NA w/o CA, $P = 0.044$, Scheffe's test.

^c Vs NA–CA, $P = 0.036$, Scheffe's test.

^d Vs before treatment, $P < 0.001$, paired t -test.

^e Vs before treatment, $P < 0.001$, paired t -test.

^f Vs before treatment, $P < 0.001$, paired t -test.

^g Vs before treatment, $P < 0.001$, paired t -test.

^h Vs NA–CA, $P = 0.002$, Scheffe's test.

ⁱ Vs NA–CA, $P = 0.022$, Scheffe's test.

^j Vs NA–CA, $P = 0.001$, Scheffe's test.

[23]. Scores below 50 indicate that health status is below the average for the general Japanese population. This method enables comparison of the magnitude of impact among the eight subscales, which in turn reflects the recommendation of the Japanese Manual of the SF-36 [23]. Scores of treated patients were compared with those of drug-naïve patients [17] and then compared with the national normative data.

Factors associated with QOL of treated patients were examined with the aid of a series of logistic regression analyses. The dependent variables were the eight subscale scores of the SF-36, which

were dichotomized at the mean of each subscale score. The independent variables were: gender; age; duration of disease morbidity; ESS score at time of the survey; experience of divorce or break up with a partner due to symptoms; experience of being forced to relocate or being dismissed due to symptoms; autonomy over control of job schedule, including the ability to take naps; and perceived support from family, friends, superiors, or coworkers. All independent variables were initially examined in univariate regression models. To control for confounding variables and to determine the main correlates, multiple logistic regression

Table 2
Sociodemographic variables of treated patients.

Characteristics	Overall	NA–CA	NA w/o CA	IHS w/o LST	Comparison between three diagnostic group
<i>Autonomy in controlling own job schedule</i>					
Yes	70.1	60.8	76.1	78.8	n.s.
No	29.9	39.2	23.9	21.2	
<i>Support from others (family, friends, superiors or coworkers)</i>					
Yes	63.8	71.1	50.0	64.8	n.s.
No	36.2	28.9	50.0	35.2	
<i>Experience of divorce or break up with partner due to symptoms (%)</i>					
Yes	10.2	11.9	4.2	13.0	n.s.
No	89.8	88.1	95.8	87.0	
<i>Experience of being forced to relocate or being dismissed due to symptoms (%)</i>					
Yes	30.3	36.1	25.0	25.9	n.s.
No	69.7	63.9	75.0	74.1	

NA–CA, narcolepsy with cataplexy; NA w/o CA, narcolepsy without cataplexy; IHS w/o LST, idiopathic hypersomnia without long sleep time; n.s., not significant.

analyses were performed for all variables. Statistical tests of the regression estimates were based on Wald statistics. Odds ratios (OR) and 95% confidence intervals (CI) were calculated in order to show associations.

3. Results

3.1. Participant characteristics

The descriptive variables for the main demographic, sociodemographic, and clinical features of the treated patients and drug-naïve patients [17] are shown in Table 1. No significant differences were found between these two groups, except for duration of disease morbidity ($t = 2.326$, $P = 0.021$).

In the treated patients, ANOVA showed that the age of onset differed significantly between the three diagnostic groups ($F[2,182] = 3.12$, $P = 0.044$). Scheffe's post-hoc test showed that the age of onset was significantly younger in patients with NA w/o CA compared with those with IHS w/o LST ($P = 0.044$). In total, 90.3% of subjects were only receiving medical treatment for daytime sleepiness, and 9.7% were receiving medical treatment for both hypersomnia and cataplexy at the time of the survey. Among the patients with NA–CA, 21.7% were receiving both stimulant and anticataplectic medications.

The ESS score before treatment differed significantly between the three diagnostic groups of treated patients ($F[2,182] = 3.94$, $P = 0.021$). Post-hoc tests revealed that the ESS score before treatment was significantly higher in the patients with NA–CA compared with those with IHS w/o LST ($P = 0.036$). However, the ESS scores were not significantly different between the patients with NA–CA and those with NA w/o CA, and between the patients with NA w/o CA and those with IHS w/o LST.

Paired t -tests revealed that ESS scores in the treated patients reduced significantly after treatment ($t = 7.19$, $P < 0.01$), and this was seen in all three diagnostic groups (NA–CA, $t = 3.82$, $P < 0.001$; NA w/o CA, $t = 4.00$, $P < 0.001$; IHS w/o LST, $t = 4.94$, $P < 0.001$). ANOVA revealed that the ESS scores after treatment differed significantly between the three diagnostic groups ($F[2,182] = 6.58$, $P = 0.002$). Post-hoc tests showed that the ESS score after treatment was significantly higher in the patients with NA–CA compared to those with IHS w/o LST ($P = 0.002$). However, there were no significant differences in the scores between the patients with NA–CA and those with NA w/o CA, and between the patients with NA w/o CA and those with IHS w/o LST.

3.2. Impact on sociodemographic status

Of the treated patients (Table 2), 70.1% had the autonomy to control their job schedule, including the ability to take naps;

63.8% perceived that they received support from their family, friends, superiors or coworkers; 30.3% had been forced to relocate or had been dismissed because of their symptoms; and 10.2% had divorced or broken up with a partner because of their symptoms.

Table 3

Short Form-36 profiles of treated patients in comparison with drug-naïve patients and national normative data: mean \pm standard deviation.

	Treated patients	Drug-naïve patients [*]	P -value [†]	P -value [‡]
Overall	$n = 185$	$n = 137$		
PF	53.2 ± 6.9	51.2 ± 8.4	0.036	<0.001
RP	40.4 ± 9.1	36.1 ± 24.5	n.s.	<0.001
BP	51.0 ± 10.3	51.0 ± 11.1	n.s.	n.s.
GH	46.9 ± 10.1	47.3 ± 10.8	n.s.	<0.001
VT	45.3 ± 10.6	43.8 ± 9.7	n.s.	<0.001
SF	46.4 ± 11.7	43.9 ± 12.6	n.s.	<0.001
RE	43.7 ± 7.4	36.5 ± 22.6	<0.001	<0.001
MH	48.2 ± 9.9	44.6 ± 10.6	0.003	0.017
NA–CA	$n = 83$	$n = 28$		
PF	52.4 ± 8.2	53.4 ± 6.1	n.s.	0.010
RP	39.8 ± 8.7	38.7 ± 23.6	n.s.	<0.001
BP	52.8 ± 10.0	53.9 ± 9.1	n.s.	0.013
GH	47.3 ± 10.4	47.9 ± 8.2	n.s.	0.021
VT	46.3 ± 11.9	45.7 ± 9.4	n.s.	0.006
SF	46.1 ± 12.3	43.1 ± 12.0	n.s.	0.005
RE	44.0 ± 7.5	39.9 ± 25.6	n.s.	<0.001
MH	47.9 ± 11.1	45.3 ± 11.6	n.s.	n.s.
NA w/o CA	$n = 48$	$n = 27$		
PF	54.7 ± 4.7	51.4 ± 5.7	n.s.	<0.001
RP	41.5 ± 11.6	33.0 ± 28.4	n.s.	<0.001
BP	49.9 ± 10.7	53.0 ± 9.7	n.s.	n.s.
GH	47.9 ± 10.5	49.0 ± 12.6	n.s.	n.s.
VT	44.7 ± 9.1	44.0 ± 9.6	n.s.	<0.001
SF	45.7 ± 11.5	45.3 ± 12.7	n.s.	0.013
RE	43.2 ± 9.2	33.4 ± 22.3	0.037	<0.001
MH	46.9 ± 9.5	45.3 ± 11.1	n.s.	0.029
IHS w/o LST	$n = 54$	$n = 82$		
PF	52.9 ± 6.1	50.5 ± 9.7	n.s.	0.001
RP	40.2 ± 6.9	36.2 ± 23.6	n.s.	<0.001
BP	49.4 ± 10.2	49.4 ± 12.0	n.s.	n.s.
GH	45.5 ± 9.3	46.5 ± 10.9	n.s.	<0.001
VT	44.4 ± 10.0	43.1 ± 9.9	n.s.	<0.001
SF	47.7 ± 11.0	43.7 ± 12.9	n.s.	n.s.
RE	43.7 ± 5.1	36.4 ± 21.7	0.004	<0.001
MH	50.1 ± 7.9	44.2 ± 10.2	<.001	n.s.

NA–CA, narcolepsy with cataplexy; NA w/o CA, narcolepsy without cataplexy; IHS w/o LST, idiopathic hypersomnia without long sleep time; PF, physical health; RP, role limitations due to physical problems; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role limitations due to emotional problems; MH, mental health; n.s., not significant.

^{*} Data from the authors' previous research (2008).

[†] Treated patients vs drug-naïve patients.

[‡] Treated patients vs national normative data.

Among the treated patients, no significant difference was found in the scores for any of the SF-36 domains between the three diagnostic groups.

3.4. Factors influencing the QOL of treated patients

Table 4 shows the results of the logistic regression analyses of all treated patients. In the final models, a higher age (OR = 1.08, 95%CI 1.01–1.16) and having no experience of being forced to relocate or being dismissed due to symptoms (OR = 2.59, 95%CI 1.15–5.82) were significantly associated with high scores on the RP subscale. The perception of support from others (OR = 3.34, 95%CI 1.18–9.50) was associated with high scores on the GH subscale. Normal ESS scores (≤ 10) (OR = 3.88, 95%CI 1.56–9.62) and having autonomy to control one's job schedule (OR = 2.48, 95%CI 1.03–5.94) were significantly associated with high scores on the VT subscale. Normal ESS scores (OR = 2.49, 95%CI 1.02–6.05) and having no experience of divorce or break up with a partner due to symptoms (OR = 9.22, 95%CI 1.05–81.11) were also significantly associated with high scores on the SF subscale.

4. Discussion

The negative impact of sleep disorders on health-related QOL has been an important issue in the field of sleep research. However, only a limited number of studies have postulated the characteristics of QOL measures of patients with hypersomnia [11–14], whereas many studies have reported the impacts of insomnia on health-related QOL [27,28]. Among these, two studies have evaluated the QOL of treated and drug-naïve patients [11,12]. However, those studies did not focus on the diagnostic categories of hypersomnia. Moreover, as indicated above, no studies have assessed the relationship between lifestyle or social support and the QOL of patients with hypersomnia. Thus, to the authors' knowledge, this is the first study to investigate the association between hypersomnia and QOL among a treated patient population with three diagnostic categories of hypersomnias of central origin, which has also considered psychosocial and environmental variables.

In this study population, subjective sleepiness manifested on the ESS decreased significantly after treatment in all three diagnostic groups. However, of note, the present study showed that the scores of many QOL domains did not differ statistically between the treated patients and the drug-naïve patients, and the scores for all of the QOL domains (except PF and BP subscales) were significantly lower in the treated patients compared with the general Japanese population. These findings are fairly consistent with the results of previous studies, in which the majority of the domain scores of treated patients were lower than general population norms [11,12]. In contrast, Beusterien et al. reported that patients with narcolepsy receiving modafinil treatment had higher scores on the RP, VT, SF, and RE subscales than placebo-treated patients at the end of a double-blind controlled trial [15]. However, the majority of SF-36 domain scores of the patients receiving modafinil treatment did not return to normal in their study.

In the study by Beusterien et al. participants who had ESS scores ≤ 8 at the end of the double-blind trial had a higher QOL than those who had ESS scores > 8 [15]. Considering this, in the present study, insufficient improvement in hypersomnia with treatment might be responsible for the lack of improvement in QOL. However, the QOL profile of treated patients did not differ between the three groups, although the ESS scores in patients with NA-CA were significantly higher compared with those with NA w/o CA or IHS w/o LST. In addition, the present study suggested that subjective sleepiness only has a partially negative impact on QOL, and this finding is in line with a previous report which indicated that subjective

sleepiness was not associated with any QOL domains in drug-naïve patients [17]. Thus, the findings of the current study, together with those of previous studies [11,12,15,17], suggest that conventional treatment with psychostimulant medications reduces the symptoms of EDS but does not normalize the general QOL of patients with hypersomnia. Factors other than subjective sleepiness could have contributed to the lower QOL among patients in the present study.

Depression has been widely accepted as an important factor that contributes to the deterioration of QOL among patients with various sleep disorders. Daniels et al. reported that depression played a role in the deterioration of QOL among treated narcolepsy patients [13]. The present study, in line with a previous study, investigated the factors responsible for the deterioration of QOL among treated patients with hypersomnia after excluding the influence of depression. However, the present study revealed that treated narcolepsy patients without depression also had poorer QOL. This finding could suggest that QOL among treated narcolepsy patients is lower regardless of the presence of depression.

Unlike a previous study [11], the present study did not find an association between the duration of disease morbidity and QOL among treated patients with hypersomnia. The reason for this phenomenon is unclear. However, it is possible that some of the patients coped with the symptoms of hypersomnia by applying behavioural strategies in order to minimize the impact of the disease on daily life.

It has been suggested that hypersomnia may interfere with career development, and may have a negative impact on income and the social status of patients [29]. Of the treated patients in the present study, 30.3% had been forced to relocate or had been dismissed because of their symptoms, which is quite compatible with previously reported results of 36.7% and 42.7% [13,14]. Furthermore, 10.2% of the patients had experienced a divorce or broken up with a partner because of their symptoms. Of note, in the current study, several QOL domains were associated with psychosocial or environmental variables, such as the experience of divorce or break up with a partner due to symptoms; being forced to relocate or being dismissed due to symptoms; having autonomy over the control of one's job schedule, including the ability to take naps; and perceived support from family, friends, superiors, and coworkers. In this regard, the impact of these psychosocial and environmental variables is thought to be stronger than the impact of disease duration or severity of subjective sleepiness. Considering this, education to increase knowledge about hypersomnia is needed in many areas of society (including the public, workplaces, schools, and healthcare settings) in order to raise awareness of hypersomnia, and to prevent social and psychological disadvantages of patients with the disorder.

This study has some limitations. First, 50 of the 83 patients with NA-CA did not undergo MSLT because they presented both typical cataplexy and SOREMPs on overnight polysomnography. For this reason, the relationship between the severity of objective sleepiness and QOL among patients with hypersomnia could not be investigated. The present study suggested that subjective sleepiness manifested on the ESS decreased significantly after treatment in all three diagnostic groups; however, further study is needed to determine whether amelioration of objective sleepiness measured with the maintenance of wakefulness test [30] is related to the improvement in QOL among patients with hypersomnia. Second, a direct comparison of SF-36 scores of patients before and after treatment could not be made. Third, in a previous report, information about psychosocial and environmental backgrounds of drug-naïve patients with hypersomnia was not obtained [17]. Therefore, the present study could not compare the factors influencing QOL between drug-naïve patients and treated patients with hypersomnia. Further prospective research on a larger sample should be

conducted in order to investigate the relationship between QOL and psychosocial and environmental variables in patients with hypersomnia so that a strategy to enhance the QOL of patients with hypersomnia be established.

5. Conclusions

In conclusion, the present study revealed that treated patients with hypersomnias of central origin have poorer QOL than the general Japanese population and drug-naïve patients. Treatment with psychostimulant medication reduced the symptoms of EDS associated with hypersomnia, but had limited effect on QOL. Psychosocial and environmental variables were associated with several QOL domains among patients with hypersomnia. The present findings suggest that an increase in understanding of hypersomnias of central origin is needed to attenuate and prevent the social and psychological disadvantages associated with these disorders.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflict of Interest associated with this article can be viewed by clicking on the following link: 10.1016/j.sleep.2011.07.014.

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Individual Traits and Environmental Factors Influencing Sleep Timing: A Study of 225 Japanese Couples

Akiko Hida,¹ Shingo Kitamura,¹ Minoru Enomoto,¹ Kentaro Nozaki,¹ Yoshiya Moriguchi,¹ Masaru Echizenya,² Hiroaki Kusanagi,² and Kazuo Mishima¹

¹*Department of Psychophysiology, National Institute of Mental Health, National Center of Neurology and Psychiatry, Tokyo, Japan,* ²*Department of Neuropsychiatry, Bioregulatory Medicine, Akita University, Graduate School of Medicine, Akita, Japan*

Behavioral and physiological processes, such as sleep-wakefulness, thermoregulation, and hormone secretion, exhibit 24-h rhythms in most organisms. These biological rhythms are driven by the circadian clock system and are entrained by the external environment, which in the case of humans includes social time schedules. Couples might be ideal experimental subjects to discriminate between individual traits and environmental factors, as they share lifestyle habits but not genetic backgrounds. In this study, sleep timing was compared between married Japanese couples ($n = 225$) who had lived together for 1 yr or more (mean 17 yrs). Additionally, the authors evaluated the influence of individual traits and environmental factors on an individual's sleep timing per each couple. The results reveal that the sleep timings of a couple are mainly associated with the chronotypes of the husband and wife, whereas the sleep timings are significantly influenced by certain environmental factors. The findings suggest that chronotype remains one of the major determinants of an individual's sleep onset and wake times. Understanding an individual's chronotype may help improve the quality of life issues surrounding sleep. (Author correspondence: mishima@ncnp.go.jp)

Keywords: Chronotype, Circadian rhythms, Lifestyle habit, Society, Spouse

INTRODUCTION

The preferred timing of daily activities shows great variation among individuals. The type of individual difference known as morningness-eveningness preference (chronotype) has been well studied by questionnaires, including the 19-item self-report Horne-Östberg Morningness-Eveningness Questionnaire (MEQ) (Horne & Östberg, 1976). Morning types fall asleep and get up earlier than intermediate types, and still earlier than evening types (Horne & Östberg, 1976; Kerkhof, 1998; Tzischinsky & Shochat, 2011). Similarly, phases of physiological rhythms, such as core body temperature and the secretion of melatonin, cortisol, or thyroid-stimulating hormone, are advanced in morning types compared to intermediate types, and more so compared to evening types (Baehr et al., 2000; Duffy et al., 1999). Another questionnaire, the Munich ChronoType Questionnaire (MCTQ), developed by Roenneberg et al. (2003), collects data on actual sleep and wake times on work days and free days, and studies by Roenneberg et al. and others have shown age- and sex-related

differences in chronotype (Adan & Natale, 2002; Carskadon et al., 1998; Randler, 2008; Roenneberg, 2004; Roenneberg et al., 2004). People have an early chronotype in childhood, which becomes later during puberty and adolescence, before returning to an earlier one, with an early sleep timing, in the late 20s. Generally, males prefer evening activities, whereas females prefer morning ones, but this sex-related difference disappears in the elderly (Foster & Roenneberg, 2008; Roenneberg et al., 2003). An individual's chronotype has also been shown to depend on dawn/dusk times, and the human circadian clock is predominantly entrained to sun time (Martinez-Nicolas et al., 2011; Roenneberg et al., 2007). These findings suggest that chronotype is associated with the circadian clock system.

The daily rhythms of behavior and physiology driven by the circadian clock system are entrained to environmental cues, such as light exposure, food intake, and work schedules, enabling us to adapt to changes in the external environment (Foster & Roenneberg, 2008; Gachon et al., 2004; Pittendrigh & Daan, 1974; Takahashi

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Address correspondence to Kazuo Mishima, MD, PhD, Director, Department of Psychophysiology, National Institute of Mental Health, National Center of Neurology and Psychiatry, 4-1-1 Ogawa-Higashi, Kodaira, Tokyo 187-8553, Japan. Tel.: +81-42-346-2071; Fax: +81-42-346-2072; E-mail: mishima@ncnp.go.jp

et al., 2008). Sleep-wake timing is one such rhythm that is influenced by both the circadian clock system and the external environment. Due to new social needs, most people in modern society are expected to adjust themselves to different time schedules (Åkerstedt et al., 2010; Wittmann et al., 2006). In this sense, environmental factors such as social time cues and lifestyle habits might strongly impact on an individual's sleep timing.

Couples might be ideal experimental subjects to discriminate between individual traits and environmental factors, as they share lifestyle habits, but not genetic backgrounds as in the case of twins (Barclay et al., 2010). Accordingly, in this study we evaluated the individual differences in sleep timing by comparing sleep onset time, wake time, and mid-sleep time between the spouses of 225 married couples who shared daily routines and housing for longer than or equal to a 1-yr period (average 17 yrs). Furthermore, we assessed the influence of individual traits (age, chronotype, and depressive mood) and environmental factors (work schedule, spouse's sleep timing, and lifestyle habits) on the determination of sleep onset and wake times.

METHODS

Subjects

The study population consisted of 225 married couples, part of a larger cohort of 1814 Japanese participants studied by Kitamura et al. (2010). The mean \pm SD age of the husbands and wives were 44.39 ± 10.69 yrs and 42.12 ± 10.05 yrs, respectively (range 22–73 yrs and 21–72 yrs, respectively). The couples had lived together for between 1 and 48 yrs (mean \pm SD: 17.04 ± 10.72 yrs), ate meals together 0–21 (mean \pm SD: 9.51 ± 4.18) times/wk, and shared a bedroom 87.11% of the time. In relation to work patterns, 43 males (19.1% of husbands) and 81 females (36.0% of wives) were nightshift workers 1–2 times/wk, 12 males (5.3% of husbands) and 22 females (9.8% of wives) 3–4 times/wk, 9 males (4.0% of husband) and 5 female (2.2% of wives) ≥ 5 times/wk. The protocol was approved by the Institutional Ethics Committee of National Center of Neurology and Psychiatry. Written informed consent was obtained from each subject. The protocol and all the procedures were in agreement with the Declaration of Helsinki and met the ethical standards of the journal (Portaluppi et al., 2010).

Self-Assessment

The Japanese versions of all the listed questionnaires were used in this study. The Horne-Östberg MEQ (Horne & Östberg, 1976) was administered to assess subjects' diurnal preferences; its validity was previously confirmed in a Japanese population (Ishihara et al., 1984). Since chronotypes have been shown to change with age, age-adjusted MEQ scores were used to rate individuals' chronotypes: age-adjusted MEQ scores of 16–41 denote evening types, 42–58 denote intermediate types, and 59–86 denote morning types. Sleep quality and

depressive mood were evaluated by the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) and the Center for Epidemiological Studies Depression Scale (CES-D) (Radloff, 1977), respectively, to assess the presence/absence of depression and sleep disorders that could strongly modify the sleep state in each subject. A PSQI total score >5 was considered indicative of poor sleep quality, and a CES-D score ≥ 16 was considered indicative of depressive symptomatology.

Statistical Analysis

Sleep onset time (SOT) and wake time (WT) for the past month were determined by the values given in the PSQI. The sleep parameters were not obtained separately for work days or free days. Mid-sleep time (MT) was calculated as the midpoint between sleep onset time and wake time. Pearson's correlation analysis was performed to ascertain whether sleep onset time, wake time, or mid-sleep time was correlated between husband and wife, and to determine if the number of years each couple lived together correlated with absolute differences between husband and wife in terms of sleep onset time (Δ SO), wake time (Δ WT), or mid-sleep time (Δ MT). Statistical analyses were performed using SPSS version 11. Noncontinuous variables were analyzed as categorical data. Full model multiple regression analysis was performed to assess the influence of individual traits and external factors on a husband's or wife's sleep timing (sleep onset time or wake time) between spouses for the 225 couples. Variables tested in the analysis for individual traits were (i) age, (ii) chronotype, and (iii) presence of depressive mood (CES-D); and for environmental factors: (i) shiftwork schedule, (ii) spouse's shiftwork schedule, (iii) spouse's sleep onset time, (iv) spouse's wake time, (v) sharing a bedroom (not a sharing a bed but sleeping in the same room as is common in Japanese culture), (vi) number of years living together, and (vii) number of times/wk eating meals (breakfast, lunch, and supper) together. The variables of "chronotype" and "presence of depressive mood" were categorized according to the cutoff points described above in the section on Self-Assessment, and the variables of "shiftwork schedule," "spouse's shiftwork schedule," and "spouse's wake time" were categorized as described above in the section on Subjects. Variables with a p value $<.05$ were considered to be statistically significant.

RESULTS

Among the total of 450 participants, 79 males (35.1% of husbands) and 62 females (27.6% of wives) were defined as morning types (M), 125 males (55.6% of husbands) and 154 females (68.4% of wives) as intermediate types (I), and 21 males (9.3% of husbands) and 9 females (4.0% of wives) as evening types (E). Fifty-six males (24.9% of husbands) and 79 females (35.1% of wives) had poor sleep quality. In addition, 40 males (17.8% of husbands) and 63 females (28.0% of wives) had depressive mood. Out of the 225 couples, 120 (53.3%) had the same chronotypes (husband and wife: 26 M-M, 93 I-I, and 1

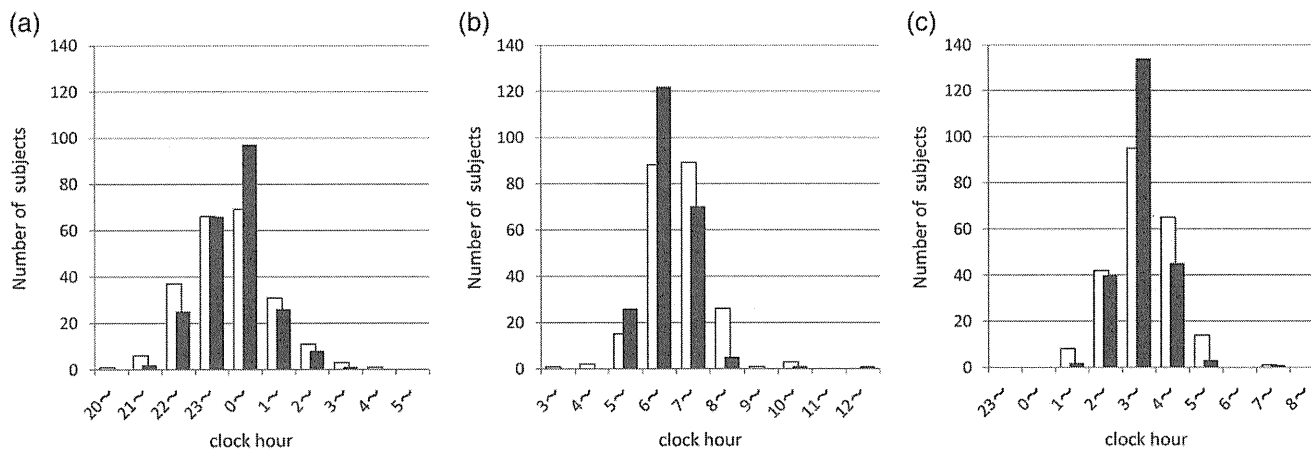


FIGURE 1. Frequency distribution of sleep onset time (A), wake time (B), and mid-sleep time (C) for 225 husbands (open bar) and their wives (black bar) in our study sample. (A) Husband's sleep onset times ranged from 19:45 to 04:00 h, whereas wife's ranged from 20:35 to 02:30 h. (B) Husband's wake times ranged from 03:00 to 10:00 h, whereas wife's ranged from 04:30 to 11:30 h. (C) Husband's mid-sleep times ranged from 00:05 to 06:45 h, whereas wife's ranged from 00:43 to 07:00 h.

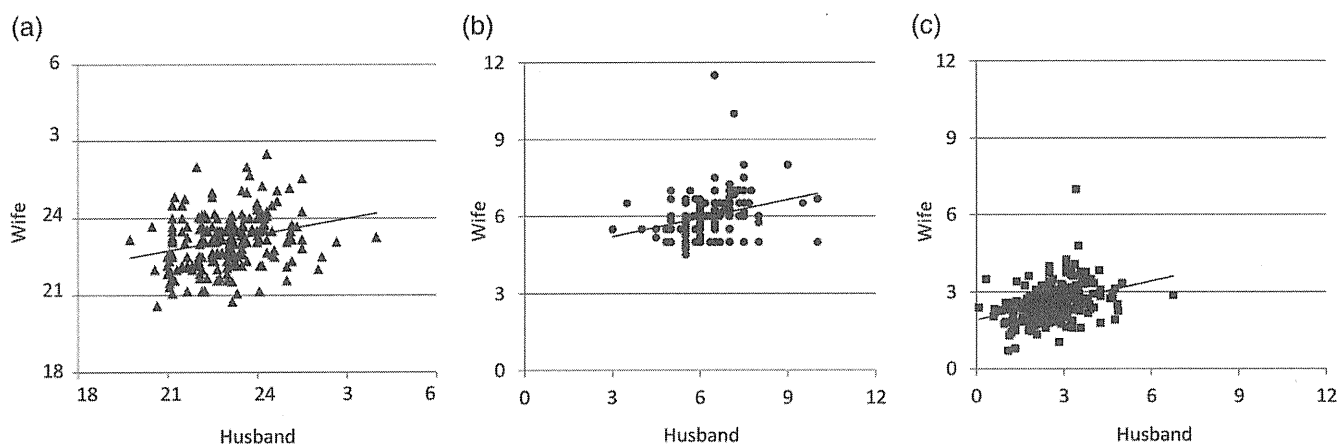


FIGURE 2. Comparison of (A) sleep onset time, (B) wake time, and (C) mid-sleep time between the husband (x-axis) and wife (y-axis) of 225 couples. Positive correlation was found between husband and wife's sleep onset times ($R = .259$, $p < .001$), wake times ($R = .285$, $p < .001$), and mid-sleep times ($R = .345$, $p < .001$).

E-E), whereas 105 (46.7%) had different chronotypes (husband and wife: 48 M-I, 5 M-E, 29 I-M, 3 I-E, 7 E-M, and 13 E-I). Couples did not differ by chronotype distribution ($\chi^2_4 = 5.30$, $p = .258$), and neither sleep quality distribution ($\chi^2_1 = .043$, $p = .837$) nor depressive mood distribution ($\chi^2_1 = .216$, $p = .642$) differed for the various combinations of chronotypes between husband and wife.

Sleep timing followed a normal distribution and varied widely among individuals (Figure 1). Husband's sleep onset time ranged from 19:45 to 04:00 h (mean \pm SD: 23:00 \pm 01:16 h), wake time from 03:00 to 10:00 h (mean \pm SD: 06:21 \pm 00:54 h), and mid-sleep time from 00:05 to 06:45 h (mean \pm SD: 02:40 \pm 00:57 h), whereas the corresponding values for the wife were 20:35 to 02:30 h (mean \pm SD: 23:08 \pm 01:01 h), 04:30 to 11:30 h (mean \pm SD: 06:01 \pm 00:46 h), and 00:43 to 07:00 h (mean \pm SD: 02:35 \pm 00:42 h). Sleep onset time, wake time, and mid-sleep time were compared between the husband and wife for each couple (Figure 2). A positive correlation was seen

between spouses for sleep onset time ($R = .259$, $p < .001$), wake time ($R = .285$, $p < .001$), and mid-sleep time ($R = .345$, $p < .001$). On the contrary, there was no correlation between spouses for age-adjusted MEQ score ($R = .078$, $p = .244$). The absolute difference between spouses in terms of SO, WT, and MT (i.e., Δ SO, Δ MT, and Δ WT) ranged from .00 to 4.75 h (mean \pm SD: 1.03 \pm .95 h), from .00 to 5.00 h (mean \pm SD: .72 \pm .77 h), and from .00 to 3.88 h (mean \pm SD: .72 \pm .65 h), respectively. No significant correlation was seen between years living together and Δ SO ($R = .069$, $p = .303$), Δ WT ($R = -.064$, $p = .341$), or Δ MT ($R = -.006$, $p = .928$) (Figure 3).

Table 1 lists the influence of individual traits and environmental factors on husband's sleep timing. Husband's SOT was mainly influenced by his chronotype, followed by number of meals/wk eaten together. Husband's SOT was not related to his age, his depressive mood, his or his wife's shiftwork schedule, wife's SOT, wife's WT, sharing a bedroom, or years living together.

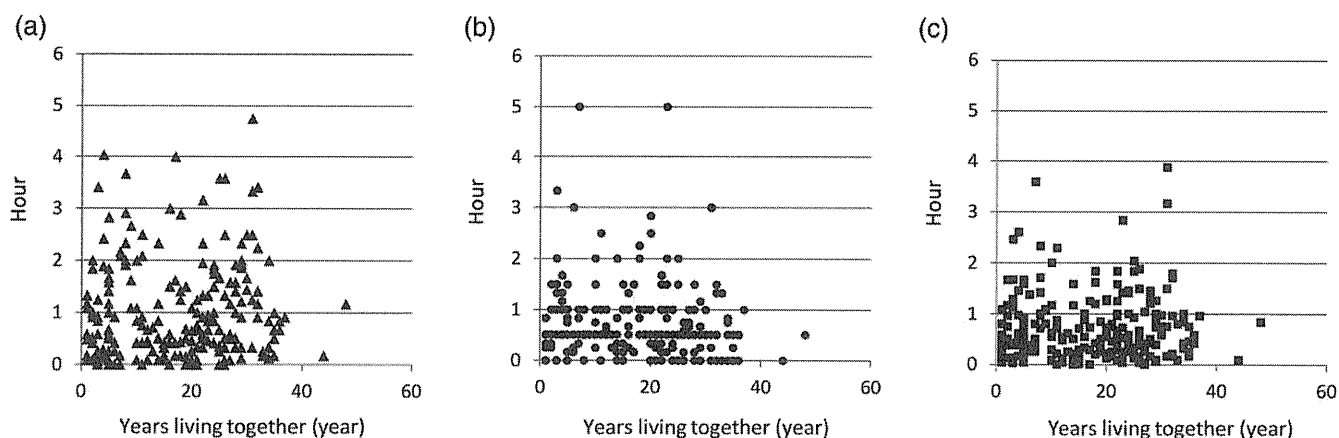


FIGURE 3. Comparison of absolute differences between husband and wife in (A) sleep onset time (Δ SO), (B) wake time (Δ WT), and (C) mid-sleep time (Δ MT) with number of years the couple had lived together. The years of living together did not correlate closely with either Δ SO ($R = .069, p = .303$), Δ WT ($R = -.064, p = .341$), or Δ MT ($R = -.006, p = .928$).

Similarly, husband's WT was mainly influenced by his own chronotype, followed by his wife's WT. No relationship was found between husband's WT and his age, his depressive mood, his or his wife's shiftwork schedule, wife's SOT, sharing a bedroom, years living together, or number of meals/wk eaten together. Overall, husband's SOT and WT were mainly and strongly associated with his chronotype.

Table 2 lists the influence of individual traits and environmental factors on wife's sleep timing. Wife's SOT was mainly influenced by her chronotype, followed

by husband's shiftwork schedule and husband's SOT. Her SOT showed no relationship with her age, her depressive mood, her shiftwork schedule, husband's WT, sharing a bedroom, years living together, or number of meal eaten times/wk together. Wife's WT was influenced mainly by her chronotype, followed by number of meals/wk eaten together and husband's WT. In contrast, wife's age, her depressive mood, her and her husband's shiftwork schedules, husband's SOT, sharing a bedroom, and years living together were not related to her WT. Overall, wife's sleep timing was

TABLE 1. Influence of individual traits and environmental factors on husband's sleep timing

Husband's sleep onset time	β	p
Age	0.199	0.195
Chronotype	0.537	<.001
Depressive mood	-0.028	0.602
Shiftwork schedule	-0.045	0.416
Wife's shiftwork schedule	-0.043	0.445
Wife's sleep onset time	0.106	0.061
Wife's wake time	0.095	0.095
Sharing bedroom	0.035	0.514
Years living together	-0.204	0.180
Meal times a week together	-0.157	0.007
$R = 0.649; F(10,214) = 15.601; p < 0.001$		
Husband's wake time	β	p
Age	-0.259	0.101
Chronotype	0.435	<.001
Depressive mood	0.078	0.155
Shiftwork schedule	0.072	0.210
Wife's shiftwork schedule	0.016	0.781
Wife's sleep onset time	0.066	0.255
Wife's wake time	0.124	0.034
Sharing bedroom	0.086	0.121
Years living together	0.130	0.404
Meal times a week together	-0.068	0.253
$R = .623; F(10,214) = 13.589; p < .001$		

Note: Boldface = significance.