### 3.3. Comparison of SF-36 scores of treated patients with those of drug-naïve patients and national norms

As there was a significant difference in the duration of disease morbidity between the treated patients and the drug-naïve patients (Table 3), analysis of covariance with disease duration as a covariate was used to examine the differences in the eight subscale scores of the SF-36 between the treated patients and the drug-naïve patients. The treated patients had significantly higher scores for the PF, RE, and MH subscales than the drug-naïve patients, and no subscale scores for the treated patients were lower than those for the drug-naïve patients. However, the treated patients had lower scores for all domains of the SF-36 compared with the national normative data, except for the PF and BP subscales.

In patients with NA–CA, no significant differences were found in the scores for any of the SF-36 domains between the treated patients and the drug-naïve patients, and the scores for all SF-36 domains (except PF, BP, and MH subscales) were significantly lower for treated patients compared with the normative data. In patients with NA w/o CA, no significant differences were found in the scores for any of the SF-36 domains (except RE subscale) between the treated patients and the drug-naïve patients, and the scores for all SF-36 domains (except for the PF, BP, and GH subscales) were significantly lower for the treated patients compared with the normative data. In patients with IHS w/o LST, although the scores for the RE and MH subscales for the treated patients were significantly higher than those for the drug-naïve patients, the scores for the RP, GH, VT, and RE subscales were lower than the normative data.

**Table 4**
Factors associated with Short Form-36 subscale scores among treated patients.

| | PF | | | RP | | | BP | | | GH | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | AOR | 95%CI | *P*-value | AOR | 95%CI | *P*-value | AOR | 95%CI | *P*-value | AOR | 95%CI | *P*-value |
| *Gender* | | | | | | | | | | | | |
| Male | | | | | | | | | | | | |
| Female | 1.53 | 0.68–3.44 | n.s. | 2.00 | 0.88–4.56 | n.s. | 0.50 | 0.23–1.08 | n.s. | 1.06 | 0.49–2.28 | n.s. |
| *Age* | | | | | | | | | | | | |
| For every increase of 1 year | 0.95 | 0.90–1.04 | n.s. | 1.08 | 1.01–1.16 | 0.025 | 0.99 | 0.93–1.04 | n.s. | 1.01 | 0.95–1.06 | n.s. |
| *Disease duration* | | | | | | | | | | | | |
| For every increase of 1 year | 0.99 | 0.94–1.05 | n.s. | 0.95 | 0.89–1.02 | n.s. | 1.01 | 0.95–1.07 | n.s. | 1.04 | 0.98–1.11 | n.s. |
| *ESS at time of survey* | | | | | | | | | | | | |
| 16–24 | | | | | | | | | | | | |
| 11–15 | 1.13 | 0.44–2.94 | n.s. | 0.88 | 0.34–2.29 | n.s. | 0.70 | 0.30–1.62 | n.s. | 0.76 | 0.30–1.96 | n.s. |
| 0–10 | 1.55 | 0.64–3.75 | n.s. | 1.76 | 0.72–4.30 | n.s. | 1.43 | 0.55–3.69 | n.s. | 1.69 | 0.72–3.97 | n.s. |
| *Autonomy to control own job schedule* | | | | | | | | | | | | |
| No | | | | | | | | | | | | |
| Yes | 1.21 | 0.52–2.83 | n.s. | 0.88 | 0.37–2.05 | n.s. | 0.83 | 0.36–1.88 | n.s. | 1.94 | 0.84–4.48 | n.s. |
| *Support from others* | | | | | | | | | | | | |
| No | | | | | | | | | | | | |
| Yes | 1.85 | 0.72–4.76 | n.s. | 0.94 | 0.36–2.46 | n.s. | 1.32 | 0.52–3.32 | n.s. | 3.34 | 1.18–9.50 | 0.023 |
| *Experience of divorce or break up with partner* | | | | | | | | | | | | |
| Yes | | | | | | | | | | | | |
| No | 1.63 | 0.38–7.06 | n.s. | 3.74 | 0.86–16.26 | n.s. | 2.53 | 0.58–10.97 | n.s. | 2.58 | 0.55–12.1 | n.s. |
| *Experience of being forced to relocate or being dismissed* | | | | | | | | | | | | |
| Yes | | | | | | | | | | | | |
| No | 1.71 | 0.76–3.86 | n.s. | 2.59 | 1.15–5.82 | 0.022 | 0.72 | 0.33–1.61 | n.s. | 1.09 | 0.49–2.43 | n.s. |
| | VT | | | SF | | | RE | | | MH | | |
| | AOR | 95%CI | *P*-value | AOR | 95%CI | *P*-value | AOR | 95%CI | *P*-value | AOR | 95%CI | *P*-value |
| *Gender* | | | | | | | | | | | | |
| Male | | | | | | | | | | | | |
| Female | 1.12 | 0.51–2.49 | n.s. | 0.56 | 0.25–1.22 | n.s. | 0.95 | 0.44–2.02 | n.s. | 0.78 | 0.36–1.71 | n.s. |
| *Age* | | | | | | | | | | | | |
| For every increase of 1 year | 0.99 | 0.94–1.05 | n.s. | 1.04 | 0.98–1.11 | n.s. | 1.01 | 0.96–1.07 | n.s. | 0.98 | 0.93–1.04 | n.s. |
| *Disease duration* | | | | | | | | | | | | |
| For every increase of 1 year | 0.97 | 0.91–1.03 | n.s. | 0.95 | 0.89–1.01 | n.s. | 1.02 | 0.96–1.08 | n.s. | 1.02 | 0.96–1.09 | n.s. |
| *ESS at time of survey* | | | | | | | | | | | | |
| 16–24 | | | | | | | | | | | | |
| 11–15 | 1.72 | 0.66–4.48 | n.s. | 1.11 | 0.43–2.86 | n.s. | 1.40 | 0.61–3.19 | n.s. | 0.89 | 0.35–2.29 | n.s. |
| 0–10 | 3.88 | 1.56–9.62 | 0.003 | 2.49 | 1.02–6.05 | 0.044 | 2.08 | 0.81–5.34 | n.s. | 1.71 | 0.71–4.10 | n.s. |
| *Autonomy to control own job schedule* | | | | | | | | | | | | |
| No | | | | | | | | | | | | |
| Yes | 2.48 | 1.03–5.94 | 0.042 | 1.65 | 0.71–3.85 | n.s. | 0.93 | 0.41–2.10 | n.s. | 1.70 | 0.72–3.98 | n.s. |
| *Support from others* | | | | | | | | | | | | |
| No | | | | | | | | | | | | |
| Yes | 2.48 | 0.89–6.44 | n.s. | 1.57 | 0.59–4.21 | n.s. | 2.17 | 0.87–5.44 | n.s. | 2.39 | 0.92–6.21 | n.s. |
| *Experience of divorce or break up with partner* | | | | | | | | | | | | |
| Yes | | | | | | | | | | | | |
| No | 1.55 | 0.38–6.34 | n.s. | 9.22 | 1.05–81.11 | 0.045 | 2.31 | 0.58–9.25 | n.s. | 0.52 | 0.12–2.27 | n.s. |
| *Experience of being forced to relocate or being dismissed* | | | | | | | | | | | | |
| Yes | | | | | | | | | | | | |
| No | 0.61 | 0.27–1.38 | n.s. | 0.98 | 0.43–2.20 | n.s. | 1.01 | 0.46–2.22 | n.s. | 0.89 | 0.40–1.97 | n.s. |

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 ESS, Epworth Sleepiess Scale; AOR, adjusted odds ratio; 95% CI, 95% confidence interval; n.s., not siginificant.

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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## References

[1] D'Alessandro R, Rinaldi R, Cristina E, Gamberini G, Lugaresi E. Prevalence of excessive daytime sleepiness an open epidemiological problem. Sleep 1995;18:389–91.
[2] Hara C, Lopes Rocha F, Lima-Costa MF. Prevalence of excessive daytime sleepiness and associated factors in a Brazilian community: the Bambui study. Sleep Med 2004;5:31–6.
[3] Ng TP, Tan WC. Prevalence and determinants of excessive daytime sleepiness in an Asian multi-ethnic population. Sleep Med 2005;6:523–9.
[4] Takegami M, Sokejima S, Yamazaki S, Nakayama T, Fukuhara S. An estimation of the prevalence of excessive daytime sleepiness based on age and sex distribution of Epworth Sleepiness Scale scores: a population based survey. [Nippon koshu eisei zasshi] Japan J Public Health 2005;52:137–45.
[5] Dauvilliers Y, Arnulf I, Mignot E. Narcolepsy with cataplexy. Lancet 2007;369:499–511.
[6] Ohayon MM, Priest RG, Zulley J, Smirne S, Paiva T. Prevalence of narcolepsy symptomatology and diagnosis in the European general population. Neurology 2002;58:1826–33.
[7] Partinen M, Hublin C. Epidemiology of sleep disorders. In: Kryger MH, Roth T, Dement WC, editors. Principles and practice of sleep medicine. Philadelphia: Saunders; 2005. p. 626–47.
[8] Honda Y. Census of narcolepsy, cataplexy and sleep life among teen-agers in Fujisawa City. Sleep Res 1979;8:191.
[9] Broughton WA, Broughton RJ. Psychosocial impact of narcolepsy. Sleep 1994;17(Suppl.):S45–9.
[10] Goswami M. The influence of clinical symptoms on quality of life in patients with narcolepsy. Neurology 1998;50(Suppl. 1):S31–6.
[11] Vignatelli L, D'Alessandro R, Mosconi P, Ferini-Strambi L, Guidolin L, De Vincentiis A, et al. Health-related quality of life in Italian patients with narcolepsy: the SF-36 health survey. Sleep Med 2004;5:467–75.
[12] Ervik S, Abdelnoor M, Heier MS, Ramberg M, Strand G. Health-related quality of life in narcolepsy. Acta Neurol Scand 2006;114:198–204.
[13] Daniels E, King MA, Smith IE, Shneerson JM. Health-related quality of life in narcolepsy. J Sleep Res 2001;10:75–81.
[14] Dodel R, Peter H, Spottke A, Noelker C, Althaus A, Siebert U, et al. Health-related quality of life in patients with narcolepsy. Sleep Med 2007;8:733–41.
[15] Beusterien KM, Rogers AE, Walsleben JA, Emsellem HA, Reblando JA, Wang L, et al. Health-related quality of life effects of modafinil for treatment of narcolepsy. Sleep 1999;22:757–65.
[16] Dauvilliers Y, Paquereau J, Bastuji H, Drouot X, Weil JS, Viot-Blanc V. Psychological health in central hypersomnias: the French Harmony study. J Neurol Neurosurg Psychiatry 2009;80:636–41.
[17] Ozaki A, Inoue Y, Nakajima T, Hayashida K, Honda M, Komada Y, et al. Health-related quality of life among drug-naive patients with narcolepsy with cataplexy, narcolepsy without cataplexy, and idiopathic hypersomnia without long sleep time. J Clin Sleep Med 2008;4:572–8.
[18] Mitler MM, Harsh J, Hirshkowitz M, Guilleminault C. Long-term efficacy and safety of modafinil (PROVIGIL®) for the treatment of excessive daytime sleepiness associated with narcolepsy. Sleep Med 2000;1:231–43.
[19] American Academy of Sleep Medi. The international classification of sleep disorders, diagnostic and coding manual. 2nd edn. Westchester, IL: American Academy of Sleep Medicine; 2005.
[20] Carskadon MA, Dement WC, Mitler MM, Roth T, Westbrook PR, Keenan S. Guidelines for the multiple sleep latency test (MSLT): a standard measure of sleepiness. Sleep 1986;9:519–24.
[21] Fukuhara S, Bito S, Green J, Hsiao A, Kurokawa K. Translation, adaptation, and validation of the SF-36 Health Survey for use in Japan. J Clin Epidemiol 1998;51:1037–44.
[22] Fukuhara S, Ware Jr JE, Kosinski M, Wada S, Gandek B. Psychometric and clinical tests of validity of the Japanese SF-36 Health Survey. J Clin Epidemiol 1998;51:1045–53.
[23] Fukuhara S, Suzukamo Y, Bito S, Kurokawa K. Manual of SF-36 Japanese Version 1.2. Tokyo: Public Health Research Foundation; 2001.
[24] Johns MW. Reliability and factor analysis of the Epworth Sleepiness Scale. Sleep 1992;15:376–81.
[25] Heponiemi T, Kouvonen A, Vanska J, Halila H, Sinervo T, Kivimäki M, et al. The association of distress and sleeping problems with physicians' intentions to change profession: the moderating effect of job control. J Occup Health Psychol 2009;14:365–73.
[26] Ho WH, Chang CS, Shih YL, Liang RD. Effects of job rotation and role stress among nurses on job satisfaction and organizational commitment. BMC Health Serv Res 2009;9:8.
[27] Leger D, Scheuermaier K, Philip P, Paillard M, Guilleminault C. SF-36: evaluation of quality of life in severe and mild insomniacs compared with good sleepers. Psychosomat Med 2001;63:49–55.
[28] Sasai T, Inoue Y, Komada Y, Nomura T, Matsuura M, Matsushima E. Effects of insomnia and sleep medication on health-related quality of life. Sleep Med 2010;11:452–7.
[29] Broughton R, Ghanem Q, Hishikawa Y, Sugita Y, Nevsimalova S, Roth B. Life effects of narcolepsy: relationships to geographic origin (North American, Asian or European) and to other patient and illness variables. Can J Neurol Sci 1983;10:100–4.
[30] Littner MR, Kushida C, Wise M, Davila DG, Morgenthaler T, Lee-Chiong T, et al. Practice parameters for clinical use of the multiple sleep latency test and the maintenance of wakefulness test. Sleep 2005;28:113–21.

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Original Article

# A two-year follow-up study on the symptoms of sleep disturbances/insomnia and their effects on daytime functioning

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ABSTRACT

*Objective:* This study attempts to identify changes in the symptoms of sleep disturbances/insomnia over a two-year course and their effects on daytime functioning.
*Methods:* We administered two population-based epidemiological surveys in 2005 and 2007 to participants from rural Japan.
*Results:* In the first survey, 30.7% of the subjects reported sleep disturbances/insomnia. Among them, 60.9% reported sleep problems at the two-year follow-up. A comparison of sleep disturbances/insomnia, and subjective daytime functioning measures between the new incident cases and persistent poor sleepers revealed that the total score of persistent poor sleepers was significantly lower than that of new incident cases on the Pittsburgh Sleep Quality Index and physical quality of life (QoL) but not mental QoL. Longitudinal comparisons of the symptoms of sleep disturbances/insomnia in persistent poor sleepers revealed that sleep efficiency was significantly worse at follow-up. Exacerbation of the symptoms of sleep disturbances/insomnia at follow-up was observed in mild but not severe cases.
*Conclusions:* Sleep efficiency progressively worsens over time, and physical QoL can deteriorate as sleep disturbances/insomnia become chronic. Since the symptoms of sleep disturbances/insomnia and their daytime effects are exacerbated even in mild cases, early intervention and treatment are necessary.


## 1. Introduction

Insomnia is a common disorder [1,2], with an estimated prevalence of about 20% among the general population [3,4]. Poor nocturnal sleep and consequent impairment in daytime functioning are the core symptoms of insomnia [5]. Indeed, both daytime impairment and night-time sleep difficulties have been established as essential items in the diagnostic criteria of insomnia by the International Classification of Sleep Disorders [6].

Several reports have described the natural course of insomnia and have revealed that a considerable number of people with insomnia exhibit a chronic course [7,8]. However, specific changes in the severity and the symptoms of the disorder as it becomes chronic have yet to be ascertained.

Previous studies on clinical populations have reported that patients with chronic insomnia commonly complain of subjective daytime impairments, including mood disturbances, concentration problems, easy fatigue, and sleepiness [5,9]. Objective measures revealed that insomnia patients show impairment in tasks that evaluate vigilance, working memory, and motor control [10,11]. These daytime dysfunctions attributed to insomnia are assumed to negatively affect sufferers' quality of life (QoL), which is a measure of general daytime functioning [12,13]. We previously reported that insomnia was generally associated with depressed mood and low QoL scores in both the mental and physical component among participants from rural Japan [14,15]. However, the precise impact of the chronicity of insomnia on QoL remains to be determined.

In order to investigate these issues, we performed a longitudinal study where a two-part questionnaire was administered at the start and end of a two-year interval to a cohort taking part in sleep studies in a single rural community [14,16,17]. Through this study, we hope to (1) elucidate the changes in insomnia symptoms over a two-year course and (2) determine the effects of chronic insomnia on daytime functioning.

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## 2. Methods

### 2.1. Participants and procedures

This survey was conducted as part of the sleep studies mentioned above in a rural town (Daisen, Tottori Prefecture, Western Japan) [14,16,17]. The Ethics Committee of Tottori University approved this study, and all participants provided written informed consent. In 2004 the total population of the town was 6643, with 5528 residents aged 20 years and above (2521 men, 3007 women), who had a mean age of 55.2 years. The first part of the questionnaire survey was administered between November 2005 and January 2006 (baseline), and the second part was administered between November 2007 and December 2007 (follow-up). With the cooperation of local public health nurses, questionnaires tagged with serial numbers were delivered to all residents aged 20 years and older during both periods. In the current study we did not distinguish nursing home respondents from hospital respondents. Responses to the questionnaire were received from 2822 people at baseline (response rate: 51%; 1222 men, 1600 women; mean age = 57.4, SD = 17.7). Two years later, the follow-up questionnaires were sent to the people who had responded at baseline, with 1577 of them responding to the follow-up questionnaire (response rate: 56%; 683 men, 894 women; mean age = 58.6, SD = 16.1) (Fig. 1). The responses to the two surveys were matched using the serial numbers.

### 2.2. Measures

The contents of the questionnaires at both baseline and follow-up were as follows:

(1) Demographic variables: The participants were asked about their age, sex, the disease currently being treated ("Please tell us the disease you are currently treated for."), family situation ("Do you currently live with your family?"), smoking habits ("Do you currently smoke?"), and alcohol consumption ("Do you drink regularly?").
(2) The Japanese version of the Pittsburgh Sleep Quality Index (PSQI) [18] was used to estimate the level of subjective sleep disturbance. The PSQI includes sub-items that evaluate sleep quality (category 1 [C1]), sleep latency (C2), sleep duration (C3), habitual sleep efficiency (C4), sleep disturbance (C5), use of sleeping medication (C6), and daytime dysfunction (C7). Although the PSQI evaluates sleep disturbances rather than insomnia, the cut-off score for insomnia has been established at 5.5 points according to a previous study [18], and we have followed that convention. Consequently, respondents with PSQI scores of 5.5 or higher were classified as people with sleep disturbances/insomnia in this study.
(3) The standardized eight-item Short Form Health Survey of the Medical Outcomes Study (SF-8) [19] was used to assess QoL. The SF-8 measures vitality, social functioning, mental health condition, emotional state, general health, physical functioning, physical state, and bodily pain. The mental component summary (MCS) scale of the SF-8 was used to evaluate mental QoL and the physical component summary (PCS) scale was used to evaluate physical QoL. The average scores for both scales for the general population were set at 50 points. There were overlapping questions regarding daytime dysfunction (C7) on the PSQI and SF-8. However, the PSQI measured daytime dysfunction with regard to sleep disturbances/insomnia, whereas the SF-8 does not make this distinction. Therefore, we analyzed the scores from the PSQI and SF-8 independently of each other.
(4) The 12-item version of the Center for Epidemiological Studies Depression Scale (CES-D) [20] was used to measure depressive symptoms. The scale has four response options: "never or rarely" (0), "sometimes" (1), "often" (2), and "always" (4). We used the total scores of CES-D as parameters of depression.

### 2.3. Statistical analysis

Student's paired *t*-tests were used to compare the PSQI, CES-D, MCS, and PCS scores between the baseline and follow-up surveys for participants who responded to both surveys.

On the basis of the results of these tests, the participants were divided into four categories: good sleepers (no insomnia symptoms at both survey periods), new incident cases (no insomnia symptoms at baseline but symptoms present at follow-up), remitted cases (insomnia symptoms at baseline but not at follow-up), and

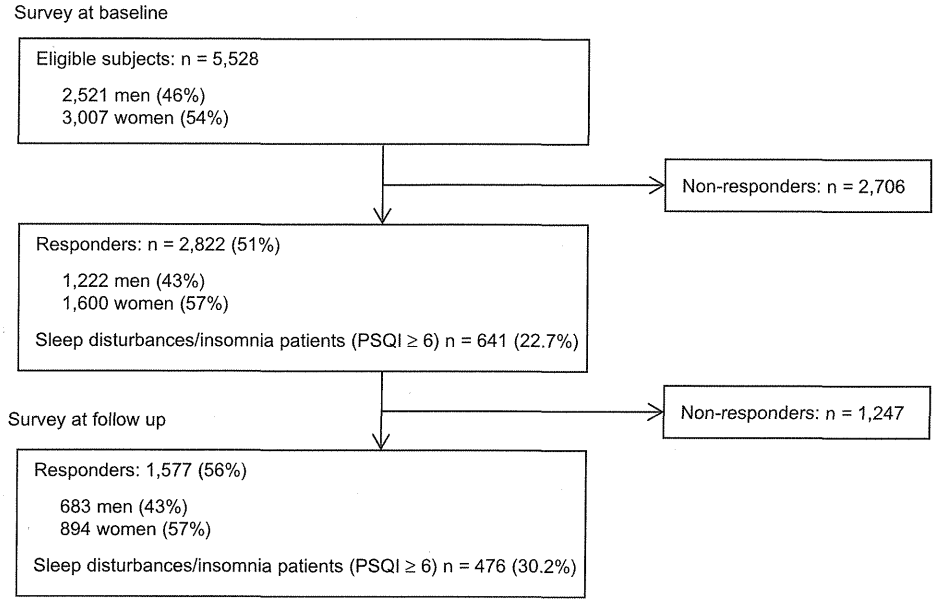



**Fig. 1.** Survey flowchart.

persistent poor sleepers (insomnia symptoms present at both survey points) [21,22]. A two-way repeated-measures analysis of variance (ANOVA) (category × survey period) was used to compare the scores of the PSQI, CES-D, and the MCS and PCS of the SF-8. The Bonferroni–Dunn test was used for post hoc analysis, and the chi-square test was performed to compare categorical variables. Student's paired *t*-tests were used to compare the PSQI, CES-D, MCS, and PCS scores between baseline and follow-up for persistent poor sleepers to reveal any changes in symptoms of sleep disturbances/insomnia and daytime functioning among people with chronic insomnia over the two-year period. A series of logistic regression analyses were conducted for subjects with insomnia/sleep disturbances at baseline to elucidate the factors associated with their persistence.

Persistent poor sleepers were further divided into two groups according to their median PSQI value at baseline (at least six but less than nine, and nine or more respectively) to determine whether the changes in the course of insomnia/sleep disturbances differed between mild and severe cases. Changes in scores of PSQI sub-items, total PSQI, CES-D, PCS, and MCS over the two-year interval were examined in these two groups by using Student's unpaired *t*-tests.

All statistical analyses were performed with SPSS Version 11.5 (SPSS Japan, Inc., Tokyo, Japan) with the alpha value set at 0.01.

## 3. Results

When the demographic data of the respondents who answered only at baseline ($n = 1247$) and those who responded at both baseline and follow-up ($n = 1577$) were compared, a significant difference was observed in age ($t$ [2394] = −3.56, $p < 0.01$), with participants in one group having a mean age of 55.9 (SD 19.6) and the other with a mean age of 58.6 (SD = 16.1). However, the difference in ages between the two groups was only 2.7 years. There were also significant differences in the number of participants who were currently receiving treatment for any disease (31.3% vs. 38.8%; $X^2$ [1] = 17.4; $p < 0.01$), and in smoking habits (26.6% vs. 18.0%; $X^2$ [1] = 30.0; $p < 0.01$). No other significant differences were found between the demographics of the two groups.

In all participants, the PSQI, CES-D, and MCS scores were slightly but significantly worse at follow-up than at baseline (PSQI: $t$ [1417] = 2.9; CES-D: $t$ [1390] = 2.9; MCS: $t$ [1373] = 2.7; $p < 0.01$ for all); there was no significant difference for PCS scores ($t$ [1373] = 2.3; not significant [ns]).

Among the participants, 56.4% were classified as good sleepers, 12.9% as new incident cases, 12.0% as remitted cases, and 18.7% as persistent poor sleepers. Table 1 shows the demographic data of the participants and the PSQI scores in each survey, and the results of the one-way ANOVA or chi-square test for each parameter of the four insomnia categories. There was no significant difference in age among the four categories ($F$ [3, 1429] = 3.9, ns). A significant difference was observed in the number of participants with insomnia who were undergoing treatment at both baseline and follow-up between the four categories (baseline: $X^2$ [3] = 15.6; follow-up: $X^2$ [3] = 18.1, $p < 0.01$ for both). Residual analysis revealed that the number of persistent poor sleepers who were undergoing treatment was significantly higher than that of other categories at both data collection periods, and that the number of good sleepers was significantly lower than that of other categories at follow-up. There was also a significant difference in the number of participants using sleep medication once or more per week at both baseline and follow-up among the four categories (baseline: $X^2$ [3] = 262.3; follow-up: $X^2$ [3] = 243.1; $p < 0.01$ for both). Residual analysis revealed that remitted cases and persistent poor sleepers had significantly higher rates of sleep medication use at baseline, and that new incident cases and persistent poor sleepers used sleep medication more often than other participants belonging to categories did at follow-up. A two-way repeated measures ANOVA (category × survey period) was performed to determine differences in total PSQI score. There were main effects for both category and survey period, and a significant interaction (main effect of category: $F$ [3, 1414] = 1188.6, $p < 0.01$; main effect of the survey period: $F$ [1, 1414] = 16.8, $p < 0.01$; and interaction between category and survey period: $F$ [3, 1414] = 429.2, $p < 0.01$). The Bonferroni–Dunn post hoc test showed that the total PSQI score was significantly worse at follow-up than at baseline for new incident cases, and significantly improved at follow-up for remitted cases, with no significant differences in the scores between the two survey points for good sleepers and persistent poor sleepers. The total PSQI score for persistent poor sleepers was significantly worse than that for good sleepers, new incident cases, and remitted cases both at baseline and at follow-up (Table 1).

### 3.1. Comparison of insomnia symptoms in the follow-up survey between new incident cases and persistent poor sleepers

PSQI scores at follow-up were compared between new incident cases and persistent poor sleepers to determine the differences in the severity of sleep disturbances/insomnia and the characteristics of the symptoms. We found that the sleep latency (C2), habitual sleep efficiency (C4), use of sleep medication (C6), and total PSQI scores of persistent poor sleepers were significantly worse than those of new incident cases (C2: $t$ [442] = 4.9; C4: $t$ [436] = 2.7; C6: $t$ [442] = 3.5; PSQI total score: $t$ [451] = 6.4, respectively, $p < 0.01$ for all) (Table 2).

The factors associated with persistent insomnia/sleep disturbances were examined with a series of univariate logistic regression analyses, performed for the 11 independent variables: age; sex; disease currently being treated; alcohol consumption; smoking habits; living status (alone or with co-habitants); sleep medication use; and CES-D, MCS, PCS, and PSQI scores at baseline. Two of these variables (living status and PSQI score) were significantly correlated with persistent poor sleepers. The adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were 3.8 (1.1–13.2) for living alone ($p < 0.01$), and 1.4 (1.3–1.6) for PSQI score ($p < 0.01$), respectively. These two variables were then analyzed with a multivariate model, which revealed that chronic insomnia/sleep disturbances were significantly associated with a higher PSQI score at baseline (OR = 1.4, 95% CI: 1.2–1.6; $p < 0.01$).

### 3.2. Comparison of daytime consequences among categories

A two-way repeated measures ANOVA (category × survey period) was conducted to compare the scores of daytime consequence measures (CES-D, MCS and PCS) at both survey periods. There were main effects of both category and survey period, and an interaction was found for CES-D (main effect of category: $F$ [3, 1387] = 119.6, $p < 0.01$; main effect of survey period: $F$ [1, 1387] = 6.8, $p < 0.01$; interaction between category and survey period: $F$ [3, 1387] = 13.8, $p < 0.01$). There was a main effect of category and an interaction between both variables for MCS and PCS (MCS: main effect: $F$ [3, 1370] = 48.5, $p < 0.01$; interaction: $F$ [3, 137] = 13.3, $p < 0.01$; PCS: main effect: $F$ [3, 1370] = 31.9, $p < 0.01$; interaction: $F$ [3, 137] = 3.9, $p < 0.01$). Post-hoc analysis confirmed that CES-D and MCS scores were significantly worse at follow-up than at baseline for good sleepers, that CES-D, MCS, and PCS scores were significantly worse at follow-up than at baseline for new incident cases, and that MCS was better at follow-up than at baseline for remitted

**Table 1**
Demographic data and PSQI scores of participants.

| At baseline | | Total ($n$ = 1434) | Without sleep disturbances/insomnia ($n$ = 994) | | With sleep disturbances/insomnia ($n$ = 440) | | |
|---|---|---|---|---|---|---|---|
| At follow up (2 years later) | | | Without sleep disturbances/ insomnia (good sleepers, $n$ = 809) | With sleep disturbances/ insomnia (new incident cases, $n$ = 185) | Without sleep disturbances/ insomnia (remitted cases, $n$ = 172) | With sleep disturbances/ insomnia (persistent poor sleepers, $n$ = 268) | $p$-Values of chi-square test or ANOVA and post hoc test among 4 sleep disturbances/insomnia groups |
| Sex (M/F) | | 633/801 | 370/439 | 72/113 | 81/91 | 110/158 | ns |
| Age, mean (SD) | | 60.2 (16.0) | 59.6 (15.9) | 59.5 (17.5) | 59.9 (15.8) | 62.8 (15.5) | ns |
| Disease currently treated, $n$ (%) | Baseline | 557 (38.9%) | 292 (36.1%) | 63 (34.1%) | 72 (41.9%) | 130 (48.5%) | Persistent poor sleepers (+) ($p$ < 0.01) |
| | Follow up | 611 (42.6%) | 314 (38.8%) | 86 (46.5%) | 69 (40.1%) | 142 (53.0%) | good sleepers (−) ($p$ < 0.01), persistent poor sleepers (+) ($p$ < 0.01) |
| Drinking habits, $n$ (%) | Baseline | 540 (37.7%) | 309 (38.2%) | 70 (37.8%) | 72 (41.9%) | 89 (33.2%) | ns |
| | Follow up | 399 (27.8%) | 227 (28.1%) | 46 (24.9%) | 58 (33.7%) | 68 (25.4%) | ns |
| Smoking habits, $n$ (%) | Baseline | 263 (18.4%) | 147 (18.2%) | 34 (18.4%) | 37 (21.5%) | 45 (16.8%) | ns |
| | Follow up | 247 (17.2%) | 136 (16.8%) | 27 (14.6%) | 39 (22.7%) | 45 (16.8%) | ns |
| Living alone, $n$ (%) | Baseline | 59 (4.1%) | 33 (4.1%) | 6 (3.2%) | 3 (1.7%) | 17 (6.3%) | ns |
| | Follow up | 62 (4.3%) | 31 (3.8%) | 7 (3.8%) | 5 (2.9%) | 19 (7.1%) | ns |
| Sleep medication use[a], $n$ (%) | Baseline | 106 (7.5%) | 2 (0.3%) | 1 (0.5%) | 26 (15.1%) | 77 (28.7%) | Good sleepers , new incident cases (−) ($p$ < 0.01), remitted cases, persistent poor sleepers (+) ($p$ < 0.01) |
| | Follow up | 120 (8.5%) | 6 (0.8%) | 31 (17.1%) | 4 (2.4%) | 79 (30.0%) | Good sleepers, remitted cases (−) ($p$ < 0.01), new incident cases, persistent poor sleepers (+) ($p$ < 0.01) |
| PSQI[b] total score, mean (SD) | Baseline | 4.6 (3.0) | 2.9 (1.5) | 3.7 (1.3)* | 7.2 (1.7)* | 8.8 (2.6) | Insomnia subcategories, survey period, interaction: $p$ < 0.01, respectively[c] |
| | Follow up | 4.8 (3.2) | 2.9 (1.5) | 7.7 (1.9)* | 3.8 (1.2)* | 9.2 (2.7) | |

SD = standard deviation, M = male, F = female, ns = not significant.
[a] Sleep medication use of once or more per week; calculated using the PSQI subitem (C6).
[b] PSQI = Pittsburgh Sleep Quality Index.
[c] Results of two-way repeated measurements ANOVA and post hoc tests.
* $p$ < 0.01.

cases ($p$ < 0.01 for all). There were no significant differences between these measures in persistent poor sleepers between baseline and follow-up. The Bonferroni–Dunn post hoc test also showed that the scores of the CES-D and PCS at follow-up in persistent poor sleepers were significantly worse than those of the other categories. In addition, MCS scores at follow-up in persistent poor sleepers were significantly worse than those of good sleepers and remitted cases. However, there was no significant difference in MCS scores at follow-up between persistent poor sleepers and new incident cases (Table 3).

**Table 2**
Comparison of sleep disturbances/insomnia symptoms at follow up between new incident cases and persistent poor sleepers.

| | New incident cases | Persistent poor sleepers | $p$-Value |
|---|---|---|---|
| C1: sleep quality | 1.5 (0.6) | 1.6 (0.6) | ns |
| C2: sleep latency | 1.5 (0.9) | 1.9 (0.9) | <0.01 |
| C3: sleep duration | 1.5 (0.8) | 1.7 (0.8) | ns |
| C4: habitual sleep efficiency | 0.8 (0.9) | 1.1 (1.1) | <0.01 |
| C5: sleep disturbance | 1.2 (0.5) | 1.3 (0.5) | ns |
| C6: use of sleeping medication | 0.5 (1.1) | 0.9 (1.3) | <0.01 |
| C7: daytime dysfunction | 0.8 (0.7) | 0.9 (0.7) | ns |
| PSQI total score | 7.7 (1.9) | 9.2 (2.7) | <0.01 |

PSQI = Pittsburgh Sleep Quality Index, Mean (standard deviation, SD), Student's $t$-test; ns = not significant.

### *3.3. Changes in the symptoms of sleep disturbances/insomnia and depression and quality of life between the two survey points in persistent poor sleepers*

The PSQI, CES-D, and QoL scores of persistent poor sleepers between baseline and follow-up were compared in order to determine changes over time in the symptoms of sleep disturbances/insomnia and their effects on daytime functioning. The results are presented in Table 4. Habitual sleep efficiency (C4) at follow-up was significantly worse than that at baseline ($t$ [255] = 3.2, $p$ < 0.01). However, there were no significant differences in scores for the other sub-items or total PSQI between the two survey periods. There were also no significant differences in CES-D, MCS, and PCS scores.

At baseline, 440 subjects reported sleep disturbances/insomnia, with 286 having a PSQI score of at least 6 but less than 9 and 154 having a PSQI score of 9 or more. The remission rate, indicated by a PSQI score of less than 6 at follow-up, was 50.3% in the former and 18.2% in the latter. The difference in remission rate between the two groups was significant ($X^2$ [1] = 43.5; $p$ < 0.01).

In order to investigate whether or not a baseline severity-dependent difference in the longitudinal course of sleep disturbances/insomnia was present, changes in PSQI, CES-D, and QoL scores were examined using the Student's unpaired $t$-test in the two groups of subjects with chronic sleep disturbances/insomnia – namely, the mild insomnia group (with a PSQI score of more than 6 but less than 9) and the severe insomnia group (with a PSQI score of 9 or more at baseline). There were significant differences be-

**Table 3**
Scores of CES-D, MSC and PCS of participants.

| At baseline | | Total ($n$ = 1,434) | Without sleep disturbances/insomnia ($n$ = 994) | | With sleep disturbances/insomnia ($n$ = 440) | | |
|---|---|---|---|---|---|---|---|
| At follow up (2 years later) | | | Without sleep disturbances/ insomnia (good sleepers, $n$ = 809) | With sleep disturbances/insomnia (new incident cases, $n$ = 185) | Without sleep disturbances/ insomnia (remitted cases, $n$ = 172) | With sleep disturbances/insomnia (persistent poor sleepers, $n$ = 268) | Results of two-way repeated measurements ANOVA and post hoc tests |
| CES-D score, mean (SD) | Baseline | 8.5 (4.8) | 7.0 (3.9)* | 8.7 (4.6)* | 10.0 (5.1) | 11.8 (5.2) | Insomnia subcategories, survey period, interaction: $p < 0.01$, respectively |
| | Follow up | 8.9 (4.7) | 7.3 (3.8)* | 10.8 (4.9)* | 8.9 (4.3) | 12.1 (5.2) | |
| MCS score, mean (SD) | Baseline | 49.9 (6.5) | 51.4 (5.4)* | 49.7 (6.6)* | 48.3 (7.2)* | 46.8 (7.4) | Insomnia subcategories, interaction: $p < 0.01$, respectively |
| | Follow up | 49.4 (6.5) | 50.8 (5.7)* | 47.0 (7.3)* | 50.0 (6.2)* | 46.8 (7.0) | |
| PCS score, mean (SD) | Baseline | 47.7 (7.0) | 49.0 (6.3) | 48.1 (7.0)* | 46.5 (7.4) | 44.6 (7.6) | Insomnia subcategories, interaction: $p < 0.01$, respectively |
| | Follow up | 47.4 (7.0) | 48.6 (6.2) | 46.3 (7.4)* | 47.1 (7.1) | 44.6 (7.8) | |

SD = standard deviation, M = male, F = female, ns = not significant, CES-D = Center for Epidemiologic Studies Depression Scale, MCS = Mental Component Summary, PCS = Physical Component Summary.
* $p < 0.01$.

tween the two groups in terms of C1, C2, C4, C5, and total PSQI scores (C1: $t$ [262] = 3.2, C2: $t$ [259] = 3.8, C4: $t$ [254] = 4.0, C5: $t$ [261] = 3.5, total PSQI score: $t$ [2566] = 6.4; $p < 0.01$ for all). However, there were no significant differences in CES-D, MCS, or PCS scores between the two groups.

## 4. Discussion

We conducted a longitudinal study over a two-year period on a rural population cohort in Japan and examined the course of sleep disturbances/insomnia symptoms and their effects on daytime functioning. The percentage of subjects with sleep disturbances/insomnia was 30.7% at baseline and 31.6% at follow-up and the number of subjects using sleep medication corresponded to the presence or absence of symptoms of sleep disturbances/insomnia at the studied points. Among the study population, the 18.7% of the subjects reported chronic sleep disturbances/insomnia (a PSQI score of greater than or equal to 5.5 in both surveys). The majority of subjects with sleep disturbances/insomnia at baseline still experienced the symptoms of sleep disturbance at follow-up (60.9%), which is consistent with previous reports [7,8]. For instance, Katz et al. showed that even in subjects with mild insomnia, 59% had sleep problems at a two-year follow-up [8]. Previous longitudinal studies on general populations showed that 40% of the individuals with insomnia at baseline had persistent symptoms [23–25]. Another study on the development of insomnia indicated that 74% of the subjects reported having insomnia symptoms for at least one year [7]. These results indicate that insomnia has a generally persistent course.

In the present study, persistent poor sleepers had the highest CES-D score among the four categories, a finding in accordance with those of previous studies [26]. A bidirectional causal relationship between depression and insomnia has been firmly established; that is, insomnia can lead to depression and vice versa [22,27,28]. Therefore, a higher CES-D score could be either a cause or a consequence of sleep disturbances/insomnia.

A recent study suggested that the persistence of insomnia was associated with the female sex, lower education level, and daytime symptoms at baseline [29]. However, these associations were not found in our study. The reason for this discrepancy is not clear. However, the fact that our sample consisted of people from a rural area and engaged in agriculture is a possible explanation [15].

In this study, the persistence of sleep disturbances/insomnia was associated with a higher PSQI score at baseline. This result suggests that severe insomnia runs a chronic course. Moreover, the sub-item scores of sleep latency, habitual sleep efficiency, sleep medication use, and total PSQI scores at follow-up were significantly worse for persistent poor sleepers than for new incident cases. In addition, habitual sleep efficiency slightly but significantly worsened over the two-year course. These findings indicate that sleep disturbances/insomnia symptoms worsen with time. In particular, the results of our cross-sectional and longitudinal analyses suggest that sleep efficiency worsens over time.

Leger et al. reported that chronic insomnia patients showed lower SF-36 scores than patients without insomnia did in all eight measures used in their study, and that the more severe the insomnia symptoms were, the worse the QoL was [30]. To the best of our knowledge, ours is the first study to describe the natural course of changes in QoL due to sleep disturbances/insomnia. Our findings revealed that persistent poor sleepers had the worst physical QoL at follow-up among the four categories and worse mental QoL compared to good sleepers and remitted cases but not new incident cases. These results suggest that physical QoL continues to deteriorate as sleep disturbances/insomnia becomes chronic, while mental QoL deteriorates when sleep disturbances/insomnia first develops but stabilizes subsequently.

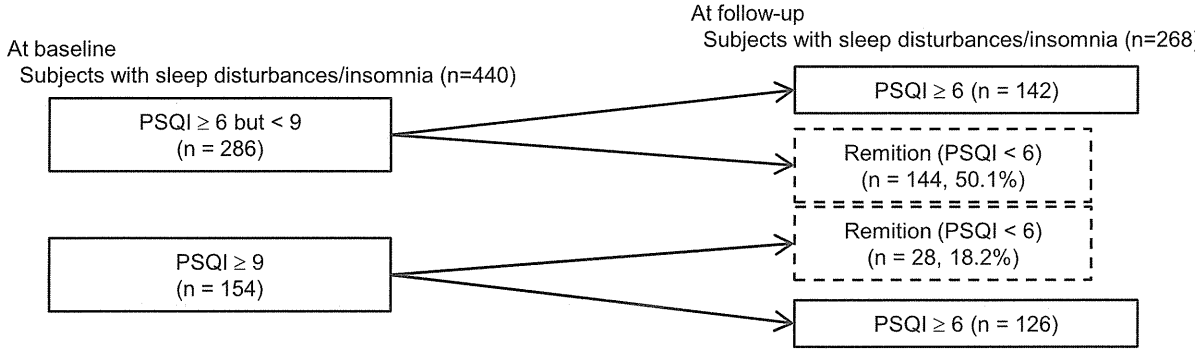
When we examined longitudinal QoL data among persistent poor sleepers, neither the MCS nor PCS scores differed significantly over the 2-year course. Thus, a modest aggravation of sleep disturbances/insomnia symptoms may not necessarily lead to a deterioration of daytime functioning over time.

A longitudinal comparison revealed significant differences in the sub-item scores of C1 (sleep quality), C2 (sleep latency), C4 (habitual sleep efficiency), C5 (sleep disturbance), and total PSQI scores between those with mild sleep disturbances/insomnia and those with severe sleep disturbances/insomnia. This suggests that mild cases can gradually worsen over time. Therefore, it is important to start an early intervention or treatment in not only patients with severe insomnia but also those with mild insomnia.

This study has several limitations. First, the response rate was approximately 50% at both survey points, with only 28.5% of the total population (baseline) responding to the follow-up questionnaire. Older, unhealthier, and non-smoking respondents may have been more compliant, thus leading to a selection bias. However, considering that the prevalence of insomnia is relatively high in el-

**Table 4**
Changes in the scores of PSQI, CES-D, MSC and PCS in subjects with PSQI ⩾ 6 but <9 at baseline and subjects compared with PSQI ⩾ 9 at baseline.

| | | Total ($n$ = 268) | Results of repeated $t$-test | PSQI ⩾ 6 but <9 at baseline ($n$ = 142) | PSQI ⩾ 9 at baseline ($n$ = 126) | Results of unpaired $t$-test*1 |
|---|---|---|---|---|---|---|
| C1: sleep quality mean (SD) | Baseline | 1.6 (0.6) | ns | 1.4 (0.5) | 1.8 (0.6) | $p < 0.01$ |
| | Follow up | 1.6 (0.6) | | 1.5 (0.6) | 1.7 (0.7) | |
| C2: sleep latency mean (SD) | Baseline | 1.8 (0.8) | ns | 1.5 (0.8) | 2.2 (0.7) | $p < 0.01$ |
| | Follow up | 1.9 (0.9) | | 1.7 (0.8) | 2.1 (0.8) | |
| C3: sleep duration mean (SD) | Baseline | 1.6 (0.8) | ns | 1.5 (0.8) | 1.8 (0.7) | ns |
| | Follow up | 1.7 (0.8) | | 1.6 (0.8) | 1.7 (0.9) | |
| C4: habitual sleep efficiency mean (SD) | Baseline | 0.8 (1.0) | $p < 0.01$ | 0.4 (0.6) | 1.3 (1.1) | $p < 0.01$ |
| | Follow up | 1.1 (1.1) | | 0.9 (1.0) | 1.3 (1.2) | |
| C5: sleep disturbance mean (SD) | Baseline | 1.3 (0.6) | ns | 1.1 (0.4) | 1.6 (0.6) | $p < 0.01$ |
| | Follow up | 1.3 (0.5) | | 1.2 (0.5) | 1.5 (0.6) | |
| C6: use of sleeping medication mean (SD) | Baseline | 0.8 (1.2) | ns | 0.4 (0.9) | 1.3 (1.4) | ns |
| | Follow up | 0.9 (1.3) | | 0.5 (1.0) | 1.4 (1.4) | |
| C7: daytime dysfunction mean (SD) | Baseline | 0.9 (0.7) | ns | 0.7 (0.6) | 1.1 (0.8) | ns |
| | Follow up | 0.9 (0.7) | | 0.8 (0.7) | 1.0 (0.7) | |
| PSQI total score mean (SD) | Baseline | 8.8 (2.6) | ns | 6.9 (0.8) | 11.0 (2.1) | $p < 0.01$ |
| | Follow up | 9.2 (2.7) | | 8.1 (2.1) | 10.4 (2.9) | |
| CES-D mean (SD) | Baseline | 11.8 (5.2) | ns | 10.3 (4.4) | 13.6 (5.5) | ns |
| | Follow up | 12.1 (5.2) | | 10.7 (4.4) | 13.5 (5.7) | |
| MCS score mean (SD) | Baseline | 46.8 (7.4) | ns | 49.3 (5.8) | 44.1 (8.0) | ns |
| | Follow up | 46.8 (7.0) | | 48.2 (6.1) | 45.2 (7.6) | |
| PCS score mean (SD) | Baseline | 44.6 (7.6) | ns | 45.7 (7.5) | 43.9 (7.4) | ns |
| | Follow up | 44.6 (7.8) | | 45.6 (7.8) | 43.4 (7.6) | |




PSQI = Pittsburgh Sleep Quality Index, CES-D = Center for Epidemiologic Studies Depression Scale, MCS = Mental Component Summary, PCS = Physical Component Summary, SD = standard deviation, ns = not significant.
*1 Results of unpaired $t$-test for differences in scores at follow up between the group with baseline total PSQI score ⩾6 but <9 and the group with the score ⩾9.

derly people and in those who have a disease, this bias might not necessarily imply an underrepresentation of insomnia patients. Second, the questionnaire did not include any measurements of socioeconomic background. Third, in the current study, the definition of sleep disturbances/insomnia was based on the PSQI cutoff established in previous studies [14–16], and the PSQI is frequently used across different ethnic groups. However, unlike the DSM-IV-TR and ICSD-II, the PSQI does not provide a clear description of the relationship between nocturnal symptoms and daytime consequences. Fourth, we classified participants into four categories on the basis of PSQI scores obtained at two survey points. However, because the follow-up survey was conducted after a relatively long interval of two years, the changes in sleep disturbances/insomnia may not have been assessed accurately as the severity of the symptoms may have fluctuated in the interval between the two data collection periods. Therefore, future studies should have closer interval assessments so that they can obtain more reliable data regarding the course of insomnia [7]. Fifth, although the follow-up duration was two years, it might have been inadequate in providing conclusive information when unaccompanied by detailed data regarding the duration of sleep disturbances/insomnia. Hence, a study over a longer period, coupled with more frequent assessments, may be necessary to draw conclusions that are more definite.

In conclusion, about 30% of our subjects had sleep disturbances/insomnia at both survey points. Among subjects with sleep disturbances/insomnia at baseline, 60.9% had chronic sleep disturbances/insomnia at follow-up. Insomnia symptoms, especially the problem of sleep efficiency, were exacerbated over time. Mental QoL was found to deteriorate when insomnia first develops but stabilizes subsequently, whereas physical QoL declines as sleep disturbances/insomnia become chronic. These findings emphasize the importance of an early intervention and treatment in not only populations with severe insomnia, but also in those with mild symptoms.

## Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: 10.1016/j.sleep.2012.05.015.

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## References


[1] Ohayon M. Epidemiological study on insomnia in the general population. Sleep 1996;19:S7–S15.
[2] Weyerer S, Dilling H. Prevalence and treatment of insomnia in the community: results from the Upper Bavarian Field Study. Sleep 1991;14:392–8.
[3] Liu X, Uchiyama M, Kim K, Okawa M, Shibui K, Kudo Y, et al. Sleep loss and daytime sleepiness in the general adult population of Japan. Psychiatry Res 2000;93:1–11.
[4] Ohayon MM. Prevalence of DSM-IV diagnostic criteria of insomnia: distinguishing insomnia related to mental disorders from sleep disorders. J Psychiatr Res 1997;31:333–46.
[5] Moul DE, Nofzinger EA, Pilkonis PA, Houck PR, Miewald JM, Buysse DJ. Symptom reports in severe chronic insomnia. Sleep 2002;25:553–63.
[6] American Academy of Sleep Medicine. International classification of sleep disorders. 2nd ed. Diagnostic and coding manual. IL, Westchester: American Academy of Sleep Medicine; 2005.
[7] Morin CM, Belanger L, LeBlanc M, Ivers H, Savard J, Espie CA, et al. The natural history of insomnia: a population-based 3-year longitudinal study. Arch Intern Med 2009;169:447–53.
[8] Katz DA, McHorney CA. Clinical correlates of insomnia in patients with chronic illness. Arch Intern Med 1998;158:1099–107.
[9] Varkevisser M, Van Dongen HP, Van Amsterdam JG, Kerkhof GA. Chronic insomnia and daytime functioning: an ambulatory assessment. Behav Sleep Med 2007;5:279–96.
[10] 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.
[11] Varkevisser M, Kerkhof GA. Chronic insomnia and performance in a 24-h constant routine study. J Sleep Res 2005;14:49–59.
[12] Leger D, Scheuermaier K, Raffray T, Metlaine A, Choudat D, Guilleminault C. HD-16: a new quality of life instrument specifically designed for insomnia. Sleep Med 2005;6:191–8.
[13] Zammit GK, Weiner J, Damato N, Sillup GP, McMillan CA. Quality of life in people with insomnia. Sleep 1999;22(Suppl. 2):S379–85.
[14] Sasai T, Inoue Y, Komada Y, Nomura T, Matsuura M, Matsushima E. Effects of insomnia and sleep medication on health-related quality of life. Sleep Med 2010;11:452–7.
[15] Komada Y, Nomura T, Kusumi M, Nakashima K, Okajima I, Sasai T, et al. Correlations among insomnia symptoms, sleep medication use and depressive symptoms. Psychiatry Clin Neurosci 2011;65:20–9.
[16] Nomura T, Inoue Y, Kusumi M, Uemura Y, Nakashima K. Prevalence of restless legs syndrome in a rural community in Japan. Mov Disord 2008;23:2363–9.
[17] Kagimura T, Nomura T, Kusumi M, Nakashima K, Inoue Y. Prospective survey on the natural course of restless legs syndrome over two years in a closed cohort. Sleep Med 2011;12:821–6.
[18] Doi Y, Minowa M, Uchiyama M, Okawa M, Kim K, Shibui K, et al. Psychometric assessment of subjective sleep quality using the Japanese version of the Pittsburgh Sleep Quality Index (PSQI-J) in psychiatric disordered and control subjects. Psychiatry Res 2000;97:165–72.
[19] Tokuda Y, Okubo T, Ohde S, Jacobs J, Takahashi O, Omata F, et al. Assessing items on the SF-8 Japanese version for health-related quality of life: a psychometric analysis based on the nominal categories model of item response theory. Value Health 2009;12:568–73.
[20] Poulin C, Hand D, Boudreau B. Validity of a 12-item version of the CES-D used in the National Longitudinal Study of Children and Youth. Chronic Dis Can 2005;26:65–72.
[21] Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? JAMA 1989;262:1479–84.
[22] Okajima I, Komada Y, Nomura T, Nakashima K, Inoue Y. Insomnia as a risk for depression: a longitudinal epidemiologic study on a Japanese rural cohort. J Clin Psychiatry 2012;73:377–83.
[23] Kim JM, Stewart R, Kim SW, Yang SJ, Shin IS, Yoon JS. Insomnia, depression, and physical disorders in late life: a 2-year longitudinal community study in Koreans. Sleep 2009;32:1221–8.
[24] Jansson-Frojmark M, Linton SJ. The course of insomnia over one year: a longitudinal study in the general population in Sweden. Sleep 2008;31:881–6.
[25] Zhang J, Lam SP, Li SX, Li AM, Lai KY, Wing YK. Longitudinal course and outcome of chronic insomnia in Hong Kong Chinese children: a 5-year follow-up study of a community-based cohort. Sleep 2011;34:1395–402.
[26] Johnson EO, Roth T, Breslau N. The association of insomnia with anxiety disorders and depression: exploration of the direction of risk. J Psychiatr Res 2006;40:700–8.
[27] Chang PP, Ford DE, Mead LA, Cooper-Patrick L, Klag MJ. Insomnia in young men and subsequent depression. The Johns Hopkins Precursors Study. Am J Epidemiol 1997;146:105–14.
[28] Breslau N, Roth T, Rosenthal L, Andreski P. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. Biol Psychiatry 1996;39:411–8.
[29] Zhang J, Lam SP, Li SX, Yu MW, Li AM, Ma RC, et al. Long-term outcomes and predictors of chronic insomnia: A prospective study in Hong Kong Chinese adults. Sleep Med 2012;13:455–62.
[30] Leger D, Scheuermaier K, Philip P, Paillard M, Guilleminault C. SF-36: evaluation of quality of life in severe and mild insomniacs compared with good sleepers. Psychosom Med 2001;63:49–55.

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# Factors Associated with Excessive Daytime Sleepiness in Obstructive Sleep Apnea Syndrome under CPAP Treatment

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## ABSTRACT

The purpose of this study was to assess factors associated with subjective sleep evaluation, chiefly excessive daytime sleepiness (EDS) in obstructive sleep apnea syndrome (OSAS) adult outpatients under continuous positive airway pressure (CPAP) treatment. One thousand and forty-eight OSAS outpatients (mean age: 51.4% male: 90.5%) who were treated by CPAP were consecutively collected. Age, sex, CPAP compliance (CPAP usage as their device of nights with application-time of at least 4 hours per night objectively; %usage ≥ 4 h/d), and Japanese version of the Pittsburgh Sleep Quality Index (PSQI-J) of the patients showing EDS (Japanese version of the Epworth Sleepiness Scale; JESS ≥ 11) were compared cross-sectionally with those of the patients who did not show EDS (JESS < 11). Nineteen point two % of all patients showed EDS subjectively. Two hundred one patients were classified to an EDS(+) group and an 847 patients were classified to EDS(–) group. Age and global PSQI-J scores were significantly different between the two groups. Logistic regression showed that EDS was significantly associated with global PSQI-J scores, but not with age. Among PSQI-J components, overall sleep quality, duration of sleep, sleep disturbance, and day dysfunction due to sleepiness were significantly higher in the EDS(+) group. Especially, 19.4% of patient in the EDS(+) group reported actual sleep time during the past month to be less than 5 hours/day. Although functional relationship should be further evaluated, insufficient sleep is the main factor associated with EDS in the OSAS patients under CPAP treatment.

**Keywords:** Obstructive Sleep Apnea Syndrome; Continuous Positive Airway Pressure; Excessive Daytime Sleepiness; Japanese Version of the Pittsburgh Sleep Quality Index (PSQI-J); Behavioral Induced Insufficient Sleep Syndrome

## 1. Introduction

Continuous positive airway pressure (CPAP) is the first-line treatment of moderate to severe obstructive sleep apnea syndrome (OSAS). The 5-year cumulative survival rates by cardiovascular disease were significantly lower in patients who did not use CPAP than in those who used the device for >6 hours/day and 1 to 6 hours/day [1]. It is undoubtedly evident that CPAP treatment for severe OSAS reduces the risk of fatal cardiovascular events [1,2]. CPAP is an effective treatment for OSAS for sleep and physical symptoms' associated with OSAS.

Effective compliance (time spent at the effective pressure) with CPAP in OSAS patients has been reported to be poor. Adequate compliance with CPAP was defined roughly as using the device for at least 4 hours 5 nights a week [3,4], the recommended standards for CPAP compliance to reduce the incidence of cardiovascular diseases [1,4]. On the other hand, any standard management, especially for the long-term management to improve excessive daytime sleepiness (EDS) determined by daytime performance and cognition does not exist. Recent meta-analyses demonstrated that CPAP elicited only small improvements in subjective sleepiness in mild to moderate OSAS, and the effects on objective sleepiness are of limited clinical significance [5]. Another meta-analysis showed that CPAP therapy does not improve general QOL scores associated with EDS, but does improve physical domains and vitality [6].

Clinically, there are many patients who despite a sig-

nificant reduction in sleep disordered breathing with good CPAP compliance show little improvement in their EDS. EDS is an important warning to the individual to stop operating because it is dangerous and life-threatening to continue without sleep, especially at risky workpalces [7]. It is important to evaluate factors other than the managements of sleep related breathing disorders and to manage the EDS caused by factors. We therefore evaluated factors associated with subjective sleep evaluation, chiefly EDS in OSAS adult outpatients under CPAP treatment.

## 2. Methods

### 2.1. Study Participants and Design

One thousand and forty-eight adult OSAS outpatients under CPAP treatment by objective monitoring regularly were consecutively collected among those regularly followed at Ohta Memorial Sleep Center, Kawasaki (**Table 1**). Every patient in whom OSAS was diagnosed went through full standard polysomnography (PSG) [8] in Jikei University School of Medicine, Tokyo or Ohta Memorial Sleep Center, Kawasaki followed by the International Classification of Sleep Disorders 2nd edition (ICSD-2) criteria [9]. Once the diagnosis of moderate to severe OSAS (apnea-hypopnea index ≥ 20) had been established, CPAP was titrated manually with full standard PSG [8]. It is generally accepted that CPAP compliance is satisfactory when the patient uses the device more than 4.5 h per night [10]. The authors defined good compliance on CPAP usage as their device for at least 70% of nights with application-time of at least 4 hours per night (%usage ≥ 4 h/d) by objective measurements [11,12] and adopted as the parameter of CPAP compliance.

In order to investigate the cross sectional relationship between CPAP compliance and subjective sleep evaluation, the authors assessed for EDS using the Japanese version of the Epworth Sleepiness Scale (JESS) [13], and for sleep quality and quantity using the Japanese version of the Pittsburgh Sleep Quality Index (PSQI-J) [14]. The authors categorized JESS total scores rating over 11 as the existence of EDS [13]. PSQI-J were compared with each component, 1) overall sleep quality (SLPQUAL); 2) sleep latency (LATEN); 3) duration of sleep (DURAT); 4) sleep efficacy (HSE); 5) sleep disturbance (DISTB); 6) needed medications to sleep (MEDS), and 7) day dysfunction due to sleepiness (DAYDYS). Each component was rated from 3 to 0, with global PSQI-J scores rating from 21 to 0 [14].

**Table 1. Demographic variables of 1048 patients under CPAP treatment.**

| | |
|---|---|
| Age (y, [range]) | 51.4 ± 12.0 [23 - 86] |
| Sex (M:F, [%male]) | 948:100 [90.5] |
| %usage ≥ 4 h/d (%, [range]) | 69.1 ± 28.3 [0.0 - 100.0] |
| Global PSQI-J scores [range] | 5.3 ± 2.9 [0 - 19] |
| JESS points [range] | 6.5 ± 4.8 [0 - 24] |

mean ± SD or N; %usage ≥ 4 h/d: CPAP usage as their device of nights with application-time of at least 4 hours per night by objective measure- ments; PSQI-J: the Japanese version of the Pittsburgh Sleep Quality Index; JESS: the Japanese version of the Epworth Sleepiness Scale.

All patients had check-ups every month after the initiation of CPAP treatment at Ohta Memorial Sleep Center, Kawasaki. In those appointments, from February 1st to April 30th in 2008, patients fulfilled JESS and PSQI-J with the assessment and monitoring objectively for CPAP use. The average use of CPAP in minutes was calculated, as was use efficacy, which refers to the proportion of time the mask was on relative to the total time the CPAP device power was on. Age, sex, %usage ≥ 4 h/d, and PSQI-J of the patients showing EDS (JESS ≥ 11) were compared with those of the patients who did not show EDS (JESS < 11), in all 1048 patients.

### 2.2. Statistical Analysis

Data were analyzed using Stat View-J5.0 for Windows [SAS Institute Inc.]. Each parameter was compared between the two groups using the unpaired T test or $\chi^2$ test. Logistic regression analysis was conducted to examine subjective excessive daytime sleepiness [EDS(+) or EDS(–)], with age, sex, %usage ≥ 4 h/d and global PSQI-J scores as independent variables. Statistical significance was determined at $P < 0.05$.

### 2.3. Approval of the Study

The study protocol was approved by the Institutional Review Boards of Ohta General Hospital. Written informed consents to participate in the study were obtained from all the participants after they were given an explanation of the study and its potential risks. All of the procedures were carried out in accordance with Good Clinical Practice, the Helsinki Declaration, and related laws.

## 3. Results

Nineteen point two % of all patients showed EDS subjectively. Two hundred one patients were classified to an EDS(+) group and an 847 patients were classified to EDS(–) group. Age and global PSQI-J scores were significantly different between the two groups (**Table 2**).

Logistic regression showed that global PSQI-J scores but not age, sex and %usage ≥ 4 h/d significantly influenced the manifestation of EDS in an independent manner (**Table 3**).

In PSQI-J components, overall sleep quality (C1), duration of sleep (C3), sleep disturbance (C5), and day dys-

function due to sleepiness (C7) were significantly different between the two groups and were worse in EDS(+) group (**Table 4**). The patients of EDS(+) group showed lower subjective sleep quality ($P < 0.001$), shorter sleep duration ($P < 0.001$), more sleep disturbed ($P < 0.001$) and more daytime dysfunction ($P < 0.001$) significantly compared with those of EDS(–) group.

Distributions of actual sleep time during the past month (PSQI-J, C3) between the EDS(+) and EDS(–) group were compared and the results are displayed with a pie graph (**Figure 1**). There is a clear tendency that percentage of shorter hour sleep is high and that of longer hour sleep is low in the EDS(+) group compared to the EDS(–) group. Especially, 19.4% of patients (n = 38) in the EDS(+) group reported actual sleep time during the past month to be less than 5 hours/day and this percentage was significantly higher than that of EDS(–) group (8.5%).

**Table 2. The Comparison of Patients Characteristics, PSQI-J between the EDS(+) and EDS(–) grou.**

| | EDS(+) JESS ≥ 11 (n = 201) | EDS(–) JESS < 11 (n = 847) | |
|---|---|---|---|
| JESS points | 14.3 ± 0.2 | 4.7 ± 0.1 | P value |
| Age (y) | 49.3 ± 0.8 | 52.0 ± 0.4 | 0.004 |
| Sex (%male) | 94.0 | 89.6 | 0.075 |
| %usage ≥ 4 h/d (%) | 66.0 ± 1.0 | 69.9 ± 2.2 | 0.077 |
| Global PSQI-J scores | 7.1 ± 0.2 | 4.9 ± 0.1 | <0.001 |

Mean ± SE P value: the unpaired T test or $\chi^2$ test, significant difference: $P < 0.05$; EDS: excessive daytime sleepiness; %usage ≥ 4 h/d: CPAP usage as their device of nights with application-time of at least 4 hours per night by objective measurements; PSQI-J: the Japanese version of the Pittsburgh Sleep Quality Index; JESS: the Japanese version of the Epworth Sleepiness Scale.

**Table 3. Multiple logistic regression analysis: influence on subjective daytime sleepiness (JESS).**

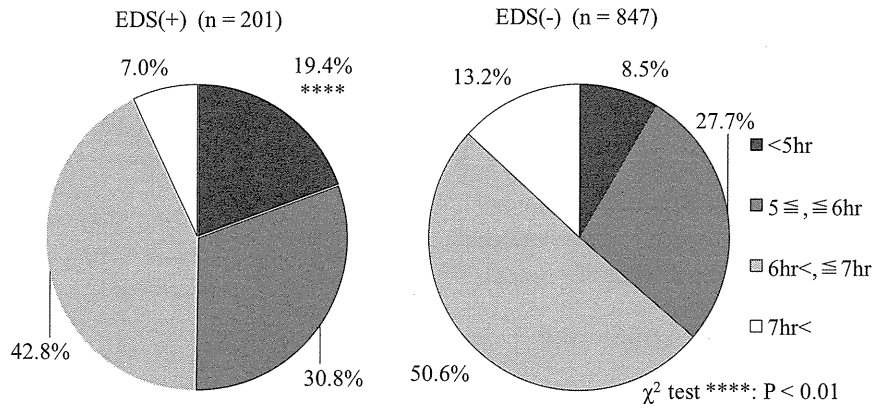
| Variable | OR (95%CI) | P value |
|---|---|---|
| Age | 0.99 (0.97 - 1.00) | 0.052 |
| Sex | 1.85 (0.94 - 3.64) | 0.074 |
| %usage ≧ 4 h/d | 1.00 (1.00 - 1.01) | 0.327 |
| global PSQI-J scores | 1.29 (1.22 - 1.36) | <0.001 |

OR: odds ratio; CI: confidence interval, significant difference: $P < 0.05$; JESS: the Japanese version of the Epworth Sleepiness Scale; %usage ≥ 4 h/d: CPAP usage as their device of nights with application-time of at least 4 hours per night by objective measurements; PSQI-J: the Japanese version of the Pittsburgh Sleep Quality Index.

**Table 4. The Comparison of PSQI-J components scores between the EDS(+) and EDS(–) group.**

| | EDS(+) JESS ≥ 11 (n = 201) | EDS(–) JESS < 11 (n = 847) | P value |
|---|---|---|---|
| C1 (SLPQUAL) | 1.5 ± 0.05 | 1.1 ± 0.02 | <0.001 |
| C2 (LATEN) | 0.7 ± 0.06 | 0.6 ± 0.03 | 0.226 |
| C3 (DURAT) | 1.6 ± 0.06 | 1.3 ± 0.03 | <0.001 |
| C4 (HSE) | 0.4 ± 0.06 | 0.3 ± 0.02 | 0.248 |
| C5 (DISTB) | 0.9 ± 0.04 | 0.7 ± 0.02 | <0.001 |
| C6 (MEDS) | 0.5 ± 0.1 | 0.3 ± 0.03 | 0.054 |
| C7 (DATDYS) | 1.6 ± 0.07 | 0.5 ± 0.02 | <0.001 |

Mean ± SE P value: the unpaired T test significant difference: $P < 0.05$; PSQI-J: the Japanese version of the Pittsburgh Sleep Quality Index; EDS: excessive daytime sleepiness; JESS: Japanese version of the Epworth Sleepiness Scale; SLPQUAL: overall sleep quality; LATEN: sleep latency; DURAT: duration of sleep; HSE: sleep efficiency; DISTB: sleep disturbance, MEDS: needed medications to sleep; DAYDYS: day dysfunction due to sleepiness.




During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.); PSQI-J: the Japanese version of the Pittsburgh Sleep Quality Index; EDS: excessive daytime sleepiness

**Figure 1. The comparison of distributions of actual sleep time during the past month (PSQI-J, C3) between the EDS(+) and EDS(–) group.**

## 4. Discussion

We found the high prevalence of EDS in the Japanese adult OSAS patients under CPAP treatment, and nearly 20% of all patients showed EDS subjectively. This appearance is high compared with previous study in the USA [15]. By subjective sleep evaluations, we found that the global PSQI-J scores were significantly higher in the adult OSAS patients under CPAP treatment with EDS than in those without EDS. In CPAP treated patients who continue to experience EDS, improving CPAP compliance is the first-line strategy [16]. We however, did not find any difference in CPAP compliance judged from %usage $\geq$ 4 h/d in the two groups. It is also well recognized that some patients continue to experience EDS even after appropriate CPAP treatment [17]. Therefore, it is important to evaluate other factors influence occurrence of EDS in CPAP treated OSA patients.

In PSQI-J component scores in the present study, overall sleep quality (C1), duration of sleep (C3), sleep disturbance (C5), and day dysfunction due to sleepiness (C7) were significantly higher in the EDS(+) group than in the EDS(–) group. It was obvious that day dysfunction due to sleepiness (C7) were more severe in the patients with EDS compared to those without EDS. It was suggested that EDS was associated with low subjective sleep quality, short sleep duration and more sleep disturbed in the patients of EDS(+) group. EDS in OSAS is not always caused by sleep apnea alone, although causative relations should further be evaluated. It should be pointed out that sleepiness is a common symptom in the general population, and often results from sleep deprivation. This type of sleepiness will not improve with CPAP if they do not have sleep disorders breathing. EDS in OSAS under good CPAP compliance may be caused clinically, by 1) development of new conditions associated with OSAS/CPAP, such as increase in weight, rhinitis or other medical illness; or 2) an undiagnosed associated condition such as poor sleep hygiene, treatment with sedating drugs, depression, or other sleep disorders; or 3) loss of placebo (honeymoon) effect revealing the conditions not previously diagnosed [10]. It was suggested that the subjective sleep evaluation, chiefly EDS, in the OSAS patients under CPAP treatment may have involved many factors surrounding the sleep habits, chiefly behaviorally induced insufficient sleep.

### 4.1. Behavioral Induced Insufficient Sleep in OSAS Patients

A common cause of EDS in OSAS patients is insufficient sleep [10], and sleep sufficiency needs to be evaluated in the patients under good CPAP compliance. Use of sleep diaries or actigraph recordings can help in assessing the sleep habits of the patients [10]. When the patient has an unusually high sleep efficacy and/or reports about 2 hours more sleep on each weekend day than each weekday, chronic sleep restriction is suspected [7]. Sleeping with the CPAP more hours will presumably result in improvements of sleepiness. According to the 2010 Nippon Hoso Kyokai (NHK) Japanese Time Use Survey [18], average sleep time per day in adult employed Japanese were 6 hours 55 minutes on weekdays, 7 hours 29 minutes on Saturday, and 7 hours 51 minutes on Sunday. Consequently, each day of the week marked the shortest sleeping hours since 1970. In a cross-sectional self-administered questionnaire survey [19], the 1-month point prevalence of poor sleep quality in Japanese white-collar daytime employees was significantly higher than in the general population of Japanese adults. Most of the OSAS patients treated by CPAP are daytime employee. The present study estimated 19.4% of the OSAS patients with EDS showed actual sleep time to be less than 5 hours/day. This duration might be equivalent to that of subjects with behaveioral induced insufficient sleep syndrome in ICSD-2 [9]. For behavioral induced insufficient sleep patients, regularizing bedtime and increasing time in bed produces a resolution of their symptoms, but no other manipulations help significantly [7,20].

### 4.2. Managements of EDS in the OSAS Patients under CPAP Treatment

Although our result pointed out that insufficient sleep is one of the most important factors affect EDS in OSAS patients, the management of EDS in the OSAS patients under CPAP treatment is a multifaceted problem including treatment, social and healthcare related factors, and these need to be discuss comprehensively. Knowledge about facilitators and barriers for adherence to CPAP treatment can be used in interventional strategies [21]. This can be increased by intensive patient education. The use of a wake-promoting medication, modafinil, is also approved for OSAS patients who are adherent to CPAP therapy but exhibit a residual EDS [22]. However, the common side effects of modafinil include headache (28%), anxiety (16%), and nervousness (14%). In addition, the possibility that addiction to modafinil may be probable [23]. Before the prescription of stimulants, it is necessary to establish an educational program for OSAS patients under CPAP treatment to enlighten what patients can do for themselves about sleep hygiene.

The limitations of the present study indicated no information about the pretreatment severity of OSAS, changes in body weight and ENT factors, the duration of CPAP use etc. and the use of only two subjective measurements, JESS and PSQI-J. In spite of these limitations, the present study supports the clinical impression that one of the most important and the first thing to manage EDS in pa-

tients under CPAP treatment is to ensure that their duration of sleep is sufficient.

## 5. Disclosure Statement

This was not an industry supported study. The authors have indicated no financial conflicts of interests.

## REFERENCES


[1] F. Campos-Rodriguez, N. Pena-Grinan, N. Reyes-Nunez, I. Cruz-Moron, J. Perez-Ronchel, F. Vega-Gallardo and A. Fernandez-Palacin, "Mortality in Obstructive Sleep Apnea-Hypopnea Patients Treated with Positive Airway Pressure," *Chest*, Vol. 128, No. 2, 2005, pp. 624-633. doi:10.1378/chest.128.2.624

[2] J. M. Marin, S. J. Carrizo, E. Vicente and A. G. Agusti, "Long-Term Cardiovasucular Outcomes in Men with Obstructive Sleep Apnea-Hypopnea with or without Treatment with Continuous Positive Airway Pressure: An Observational Study," *Lancet*, Vol. 365, No. 9464, 2005, pp. 1046-1053.

[3] N. B. Kribbs, A. I. Pack, L. R. Kline, P. L. Smith, A. R. Schwartz, N. M. Schubert, S. Redline, J. N. Henry, J. E. Getsy and D. F. Dinges, "Objective Measurement of Patterns of Nasal CPAP Use by Patients with Obstructive Sleep Apnea," *American Journal of Respiratory and Critical Care Medicine*, Vol. 147, No. 4, 1993, pp. 887-895.

[4] M. Orth, S. Kotterba, J. W. Walther, K. Rasche, G. Schultze-Werninghaus and H. W. Duchna, "Long Term Compliance of CPAP-Therapy-Update, Predictors and Interventions," *Pneumologie*, Vol. 60, No. 8, 2006, pp. 480-484. doi:10.1055/s-2006-944234

[5] N. S. Marshall, M. Barnes, N. Travier, A. J. Campbell, R. J. Pierce, R. D. McEvoy, A. M. Neill and P. H. Gander, "Continuous Positive Airway Pressure Reduces Daytime Sleepiness in Mild to Moderate Obstructive Sleep Apnea: A Meta-Analysis," *Thorax*, Vol. 61, No. 5, 2006, pp. 430-434. doi:10.1136/thx.2005.050583

[6] J. Jing, T. Huang, W. Cui and H. Shen, "Effect on Quality of Life of Continuous Positive Airway Pressure in Patients with Obstructive Sleep Apnea Syndrome: A Meta-Analysis," *Lung*, Vol. 186, No. 3, 2008, pp. 131-144. doi:10.1007/s00408-008-9079-5

[7] T. Roehrs, M. Carscadon, W. C. Dement and T. Roth, "Daytime Sleepiness and Alertness," In: M. H. Kryeger, T. Roth and W. C. Dement, Eds., *Principles and Practice of Sleep Medicine*, 5th Edition, Elsevier Sanders, Philadelphia, 2011, pp. 42-53. doi:10.1016/B978-1-4160-6645-3.00004-9

[8] D. Hailey, K. Tran, R. Dales, S. Mensinkai and L. McGahan, "Recommendations and Supporting Evidence in Guideline for Referral of Patients to Sleep Laboratories," *Sleep Medicine Review*, Vol. 10, No. 4, 2006, pp. 287-299. doi:10.1016/j.smrv.2005.10.004

[9] American Academy of Sleep Medicine, "The International Classification of Sleep Disorders 2nd Edition (ICSD-2), Diagnostic and Coding Manual," American Academy of Sleep Medicine, Westchester, 2005.

[10] J. Santamaria, A. Iranzo, J. Ma Montserrat and J. Pablo, "Persistent Sleepiness in CPAP Treated Obstructive Sleep Apnea Patients: Evaluation and Treatment," *Sleep Medicine Review*, Vol. 11, No. 3, 2007, pp. 195-207. doi:10.1016/j.smrv.2007.02.005

[11] H. M. Engleman, S. E. Martin, I. J. Deary and N. J. Douglas, "Effect of Continuous Positive Airway Pressure Treatment on Daytime Function in Sleep Apnea/Hypopnea Syndrome," *Lancet*, Vol. 343, No. 8897, 1994, pp. 572-575. doi:10.1016/S0140-6736(94)91522-9

[12] J. L. Perin, J. Krieger, D. Rodenstein, A. Cornette, E. Sforza, P. Delguste, C. Deschaux, V. Grillier and P. Levy, "Effectiveness Compliance during the First 3 Months of Continuous Positive Airway Pressure: A European Prospective Study of 121 Patients," *American Journal of Respiratory and Critical Care Medicine*, Vol. 160, No. 4, 1999, pp. 1124-1129.

[13] M. Takegami, Y. Suzukamo, T. Wakita, H. Noguchi, K. Chin, H. Kadotani, Y. Inoue, Y. Oka, T. Nakamura, J. Green, M. W. Johns and S. Fukuhara, "Development of a Japanese Version of the Epworth Sleepiness Scale (JESS) Based on Item Response Theory," *Sleep Medicine*, Vol. 10, No. 5, 2009, pp. 556-565. doi:10.1016/j.sleep.2008.04.015

[14] Y. Doi, M. Minowa, M. Uchiyama, M. Okawa, K. Kim, K. Shibui and Y. Kamei, "Psychometric Assessment of Subjective Sleep Quality Using the Japanese Version of the Pittsburgh Sleep Quality Index (PSQI-J) in Psychiatric Disordered and Control Subjects," *Psychiatry Research*, Vol. 97, No. 2, 2000, pp. 165-172. doi:10.1016/S0165-1781(00)00232-8

[15] C. Guilleminault and P. Philip, "Tiredness and Somnolence Despite Initial Treatment of Obstructive Sleep Apnea Syndrome (What to Do When an OSAS Patient Stays Hypersomnolent Despite Treatment)," *Sleep*, Vol. 19, No. 9S, 1996, pp. 117-122.

[16] M. K. Reeves-Hoche, R. Meck and C. W. Zwillich, "Nasal CPAP, an Objective Evaluation of Patient Compliance," *American Journal of Respiratory and Critical Care Medicine*, Vol. 149, No. 1, 1994, pp. 149-154.

[17] M. A. Bédard, J. Montplaisir, J. Malo, F. Richer and I. Rouleau, "Persistent Neuropsychological Deficits and Vigilance Impairment in Sleep Apnea Syndrome after Treatment with Continuous Positive Airways Pressure (CPAP)," *Journal of Clinical and Experimental Neuropsychology*, Vol. 15, No. 2, 1993, pp. 330-341. doi:10.1080/01688639308402567

[18] T. Kobayashi, E. Morofuji and Y. Watanabe, "Sleeping Time Keeps Decreasing, Male Housework Time Is Increasing. From the 2010 NHK Japanese Time Use Survey," The NHK Monthly Report on Broadcast Research, 2011, pp. 2-21.

[19] Y. Doi, M. Minowa and T. Tango, "Impact and Correlates of Poor Sleep Quality in Japanese White-Collar Employees," *Sleep*, Vol. 26, No. 4, 2003, pp. 467-471.

[20] H. P. Van Dongen, G. Maislin, J. M.Mullington and D. F. Dinges, "The Cumulative Cost of Additional Wakefulness: Dose-Response Effects on Neurobehavioral Functions and Sleep Physiology from Chronic Sleep Restriction and Total Sleep Deprivation," *Sleep*, Vol. 26, No. 2, 2003, pp. 117-126.

[21] A. Golay, A. Girard, S. Grandin, J. C. Metrailler, M. Victrion, P. Lebas, J. Ybarra and T. Rochat, "A New Educational Program for Patients Suffering from Sleep Apnea Syndrome," *Patient Education and Counseling*, Vol. 60, No. 2, 2006, pp. 220-227. doi:10.1016/j.pec.2005.01.007

[22] J. E. Black and M. Hirshkowitz, "Modafinil for Treatment of Residual Excessive Sleepiness in Nasal Continuous Positive Airway Pressure-Treatment Obstructive Sleep Apnea/Hypopnea Syndrome," *Sleep*, Vol. 28, No. 4, 2005, pp. 464-471.

[23] W. Charles, Atwood Jr., J. Patrick and R. Givelber, "Medical Therapy for Obstructive Sleep Apnea," In: M. H. Kryeger, T. Roth and W. C. Dement, Eds., *Principles and Practice of Sleep Medicine*, 5th Edition, Elsevier Sanders, Philadelphia, 2011, pp. 1219-1232.

# Brief Behavioral Therapy for Refractory Insomnia in Residual Depression: An Assessor-Blind, Randomized Controlled Trial

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## ABSTRACT

***Objective:*** Insomnia often persists despite pharmacotherapy in depression and represents an obstacle to its full remission. This study aimed to investigate the added value of brief behavioral therapy for insomnia over treatment as usual (TAU) for residual depression and refractory insomnia.

***Method:*** Thirty-seven outpatients (mean age of 50.5 years) were randomly assigned to TAU alone or TAU plus brief behavioral therapy for insomnia, consisting of 4 weekly 1-hour individual sessions. The Insomnia Severity Index (ISI) scores (primary outcome), sleep parameters, and GRID-Hamilton Depression Rating Scale (GRID-HAMD) scores were assessed by blind raters and remission rates for both insomnia and depression were collected at 4- and 8-week follow-ups. The patients were recruited from February 18, 2008, to April 9, 2009.

***Results:*** Brief behavioral therapy for insomnia plus TAU resulted in significantly lower ISI scores than TAU alone at 8 weeks ($P < .0005$). The sleep efficiency for the combination was also significantly better than that for TAU alone ($P = .015$). Significant differences were observed in favor of the combination group on both the total GRID-HAMD scores ($P = .013$) and the GRID-HAMD scores after removing the 3 sleep items ($P = .008$). The combination treatment produced higher rates of remission than TAU alone, both in terms of insomnia (50% vs 0%), with a number needed to treat (NNT) of 2 (95% CI, 1–4), and in terms of depression (50% vs 6%), with an NNT of 2 (95% CI, 1–5).

***Conclusions:*** In patients with residual depression and treatment refractory insomnia, adding brief behavioral therapy for insomnia to usual clinical care produced statistically significant and clinically substantive added benefits.

***Trial Registration:*** clinicaltrials.gov Identifier: NCT00610259

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Insomnia occurs in 80%–90% of patients with untreated major depression.[1–3] Insomnia concurrent with depression not only is a major source of subjective distress but also most likely interacts with other depressive symptoms so as to confer greater illness severity.[4–6] Further, insomnia not only is the most likely symptom to persist following treatment[2,7] but also may constitute an obstacle for patients to achieve full remission and recovery,[8–10] and its persistence may serve as a risk factor for relapse.[11] Thus, insomnia is no longer considered a simple accompanying symptom of depression but is regarded as a comorbid disorder. Given this shift in perspective, it follows that it may be useful to provide targeted treatment for the insomnia that occurs in the context of depression.

To date, there have been two trials that evaluate how insomnia treatment can be combined with traditional antidepressant therapies: one with pharmacotherapy[12] and one with cognitive-behavioral therapy for insomnia.[13] A multicenter randomized controlled trial (RCT)[12] has found that adding a hypnotic to antidepressant treatment led to improvement in both sleep and depression. However, 50% and 58% of patients treated with the combination therapy were still nonremitters in terms of insomnia and depression, respectively, at the end of the trial. The cognitive-behavioral therapy for insomnia is based on a multicomponent approach that includes several modules,[14] including sleep hygiene education, sleep restriction, and stimulus control as first-line interventions and cognitive therapy, relaxation training, and sleep compression as adjunctive ones.[15] For primary insomnia, the efficacy of cognitive-behavioral therapy for insomnia has been well established.[16,17] For comorbid insomnia in depression, there has been only one trial[13] of cognitive-behavioral therapy for insomnia, which investigated the efficacy of adding 7-session individual cognitive-behavioral therapy for insomnia to antidepressant pharmacotherapy in acute phase treatment. The combination therapy achieved remission rates of 50% for insomnia and 62% for depression.

Neither of these two trials, however, included patients with depression and insomnia refractory to adequate pharmacotherapy.[12,13] Thus, effective treatment is needed for insomnia in depression, especially one that persists after adequate pharmacotherapy. In the present study, we aimed to develop a brief behavioral therapy for insomnia by focusing on core components of cognitive-behavioral therapy for insomnia and to conduct an RCT to examine its effectiveness when added to treatment as usual (TAU), in comparison with TAU alone, for residual depression with refractory insomnia.

## METHOD

### Participants

Patients were recruited from February 18, 2008, to April 9, 2009, at 3 psychiatric outpatient departments in Japan.

We aimed to include patients with currently partially remitted, mild, or moderate depression, who presented with significant insomnia, despite

adequate pharmacologic treatment. Inclusion criteria were outpatients who (1) had *DSM-IV* major depressive disorder, as diagnosed by the Structured Clinical Interview for *DSM-IV* (SCID)[18]; (2) were aged between 20 and 70 years; (3) for the index episode, had already been on maximum doses of 2 types of antidepressants for at least 4 weeks each (depression is usually regarded resistant or refractory when at least 2 trials with antidepressants from different pharmacologic classes fail to produce a significant clinical improvement[19]); (4) had a score of 2 on at least 1 of the 3 sleep items of the GRID-Hamilton Depression Rating Scale (GRID-HAMD),[20] which has explicit anchor points for each assessment item and has excellent interrater validity among even untrained raters[21]; (5) had a score of 8 or more on the Insomnia Severity Index (ISI),[14,22,23] which is now considered a standard measure of the global severity of insomnia and is used in many studies[12,13,24] (the total score of 8–14 indicates subthreshold insomnia and 15–28, clinical insomnia); and (6) had a score between 8 and 23 on the 17-item GRID-HAMD, representing current subthreshold to moderate depression.[25]

Exclusion criteria were (1) mental or physical status requiring hospitalization; (2) serious suicidal risk; (3) having had or currently receiving any structured psychotherapy; (4) current diagnosis of primary anxiety or personality disorder, substance abuse or dependence, or psychosis; a history of schizophrenia or bipolar disorder; or significant medical problems; (5) duration of depression shorter than 2 months; (6) insomnia possibly being due to sleep apnea or periodic limb movements during sleep. Possible sleep apnea was assessed by using the Berlin Questionnaire[26]; (7) engaging in work involving night-shift; and (8) patients currently taking methylphenidate or modafinil. Any other psychotropic medications, including antidepressants and hypnotics, and prescriptions for medical conditions were allowed.

### Study Design

Assessor-blind, individually randomized, parallel-group trial design was employed. An independent statistician generated the random allocation sequences by the computer, using variable blocks and stratified by the severity of depression (the total GRID-HAMD score of 14 or more, or less than 14) and by study sites. Allocation sequences were kept centrally, and the allocation was provided by facsimile to each site upon notification of a patient's enrollment.

Participants were randomized to brief behavioral therapy for insomnia plus TAU or TAU alone. Neither patients nor physicians of TAU were blind to allocation. However, all patients were requested not to reveal their allocated treatment to the assessors for the GRID-HAMD. After each assessment, an assessor guessed which group the patient had been assigned to, making it possible to examine if the blinding was successful.

### Assessment Measures

Patients were assessed at baseline and at 4 and 8 weeks. Patients who dropped out of the intervention were asked to complete the assessments.

The primary outcome was the total ISI score at 8 weeks. The secondary outcomes were the total 17-item GRID-HAMD score and the 14-item GRID-HAMD score (excluding the 3 sleep items) at 4 and 8 weeks. The interrater reliability of the GRID-HAMD was calculated by audiotaping assessment sessions and having another rater assess the recordings independently. The secondary outcomes for sleep included the ISI score at 4 weeks and the Pittsburgh Sleep Quality Index (PSQI)[27,28] score, the sum of the 3 sleep items on the GRID-HAMD, and sleep parameters, such as sleep efficiency, total sleep time, sleep onset latency, time wake after sleep onset, collected through the PSQI, at 4 and 8 weeks. These sleep parameters are thought to enable quantification of the presenting sleep complaint.[14] Sleep diaries were employed only in the intervention arm as one of the active treatment components and thus not used to collect sleep parameters.

Dichotomous outcomes were also considered. Patients were considered as remitters for insomnia if their ISI score was less than 8[24] and as remitters for depression if their 17-item GRID-HAMD score was less than 8.[25] If any unfavorable event (ie, suicidal attempt, death, hospital admission) occurred during the study period, it was reported. All antidepressant and hypnotic dosages were converted into defined daily dose[29] and summed.

### Sample Size

Sample size was based on a power analysis conducted for the ISI scores. Effect sizes were estimated from previous studies on insomnia in depression (a Cohen *d* of 0.95 on the ISI total scores at posttreatment between the combined escitalopram plus cognitive-behavioral therapy for insomnia arm and the escitalopram plus pseudodesensitization arm[30] and a Cohen *d* of 1.81 in sleep efficiency pre– to post–cognitive-behavioral therapy for insomnia[31]) and from brief behavioral therapy for insomnia pilot data from our group acquired prior to this study (the mean change in the ISI scores pretreatment to posttreatment was 6.75 in 4 patients). The mean ± SD change in the ISI scores pretreatment to posttreatment was estimated to be 6 ± 3 for the brief behavioral therapy for insomnia plus TAU group and 2 ± 3 for the TAU group. With 0.9 power to detect a significant difference at $P = .05$ (2-sided), it was calculated that 12 patients would be required for each arm. Thus, allowing for a 30% dropout rate, 18 participants would need to be recruited per group.

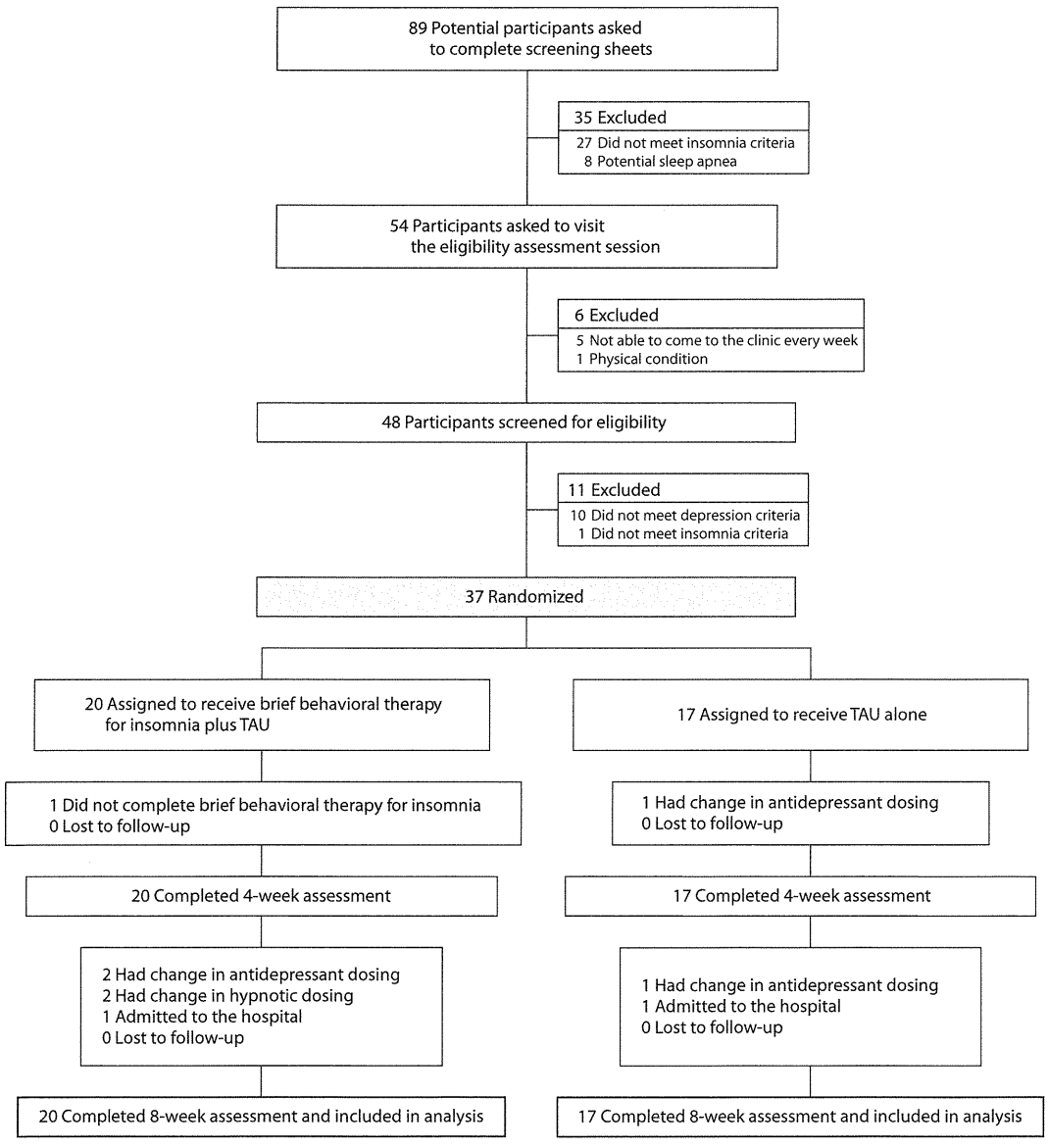
### Trial Interventions

The treatment regimen for the present study was developed and highly structured based on a published treatment manual for cognitive-behavioral therapy for insomnia[15] and was provided to therapists as a written manual. The program consisted of 4 weekly individual sessions, each lasting approximately 50 minutes (Table 1). The number of the sessions, while fewer than traditional cognitive-behavioral therapy for insomnia[15] and those in the previous studies,[13,24] is nevertheless in keeping with (1) the finding that 4 sessions may constitute the optimal dose for cognitive-behavioral therapy for insomnia[32] and (2) recent studies showing the

**Table 1. Overview of Principles in Treatment Sessions in the Brief Behavioral Therapy for Insomnia Condition**

| Session | Module | Description |
|---|---|---|
| 1 | Sleep diary | The aim is to increase patients' awareness of their own maladaptive sleep habits, thus paving the way for the correction of these habits. In addition, the sleep diary allows both the patient and the clinician to gather the data needed to measure and guide treatment |
| | Sleep hygiene education | The patient learns about the impact of lifestyle habits, such as exercise; diet and alcohol use; and the influence of environmental factors, such as light, noise, and temperature in the bedroom |
| 2 | Introduction of the behavioral model of insomnia | Discussion of predisposing, precipitating, and perpetuating factors of patient's insomnia. Presenting the perspective to the patient so that he or she understands why the interventions may benefit, which is thus likely to enhance adherence |
| | Sleep restriction | Involves a strict schedule of bed times and rising times, restricting patients' allowed time in bed to the actual sleeping time according to the patients' sleep diary; the aim is to increase homeostatic sleep drive through partial sleep deprivation |
| | Stimulus control | The aim is to break associations between the sleep environment and wakefulness by teaching the participant not to engage in bedroom activities incompatible with sleep and to stay in bed only when asleep or sleepy |
| 3 | Sleep titration | The objective is to assess treatment gains and compliance and to make adjustments to the patient's sleep schedule according to a weekly average sleep efficiency |
| 4 | Sleep titration | Same as above |
| | Relapse prevention | Involves a review of how insomnia started and how it maintained over time. Afterward, discussion about the approach to maintaining clinical gains in the long run and what to do when insomnia recurs |

**Figure 1. Participant Flow Diagram**




Abbreviation: TAU = treatment as usual.

**Table 2. Sociodemographic and Clinical Characteristics of Participants**

| Characteristic | Brief Behavioral Therapy for Insomnia + TAU (n = 20) | TAU Alone (n = 17) | All Participants (N = 37) |
|---|---|---|---|
| Age, mean (SD), y | 52.9 (11.6) | 47.8 (10.1) | 50.5 (11.1) |
| Sex, n (%) | | | |
| Female | 15 (75.0) | 8 (47.1) | 23 (62.2) |
| Male | 5 (25.0) | 9 (52.9) | 14 (37.8) |
| Education, n (%) | | | |
| < High school | 3 (15.0) | 0 (0.0) | 3 (8.1) |
| High school diploma | 12 (60.0) | 9 (52.9) | 21 (56.8) |
| Some college or university | 5 (25.0) | 7 (41.2) | 12 (32.4) |
| Postgraduate degree | 0 (0.0) | 1 (5.9) | 1 (2.7) |
| Occupation, n (%) | | | |
| Employed, full time | 3 (15.0) | 6 (35.3) | 9 (24.3) |
| Employed, part time | 3 (15.0) | 3 (17.6) | 6 (16.2) |
| Homemaker | 11 (55.0) | 5 (29.4) | 16 (43.2) |
| Unemployed | 3 (15.0) | 3 (17.6) | 6 (16.2) |
| Marital status, n (%) | | | |
| Married | 15 (75.0) | 8 (47.1) | 23 (62.2) |
| Divorced or widowed | 3 (15.0) | 5 (29.4) | 8 (21.6) |
| Single | 2 (10.0) | 4 (23.5) | 6 (16.2) |
| Duration of index episode, mean (SD), mo | 21.3 (16.9) | 30.4 (45.7) | 25.5 (33.2) |
| Duration of treatment for index episode, mean (SD), mo | 18.1 (11.1) | 27.8 (46.5) | 22.5 (32.4) |
| No. of depressive episodes, mean (SD) | 2.0 (1.0) | 1.5 (0.7) | 1.8 (0.9) |
| Habitual alcohol intake, n (%) | 1 (5.0) | 2 (11.8) | 3 (8.1) |
| Total antidepressant usage, mean (SD), DDD | 1.7 (0.9) | 1.5 (0.9) | 1.6 (0.9) |
| TCA usage, mean (SD), DDD | 0.1 (0.4) | 0.1 (0.2) | 0.1 (0.3) |
| SSRI usage, mean (SD), DDD | 1.0 (0.8) | 0.9 (1.1) | 0.9 (0.9) |
| SNRI usage, mean (SD), DDD | 0.3 (0.8) | 0.1 (0.1) | 0.2 (0.6) |
| Other usage, mean (SD), DDD | 0.2 (0.1) | 0.4 (0.5) | 0.3 (0.4) |
| Hypnotic usage, mean (SD), DDD | 0.7 (0.9) | 1.1 (0.7) | 0.9 (0.8) |
| Insomnia Severity Index score, mean (SD) | 15.3 (4.7) | 17.4 (3.3) | 16.3 (4.2) |
| Pittsburgh Sleep Questionnaire Index score, mean (SD) | 12.5 (2.8) | 13.8 (3.0) | 13.1 (2.9) |
| Subjective sleep parameters, mean (SD) | | | |
| Sleep efficiency, mean (SD), % | 66.4 (14.3) | 67.7 (14.0) | 67.0 (14.0) |
| Total sleep time, min | 312.0 (111.1) | 283.5 (66.5) | 298.9 (93.2) |
| Sleep onset latency, min | 55.8 (50.8) | 58.3 (54.4) | 56.9 (51.7) |
| Wake after sleep onset, min | 104.0 (85.8) | 88.2 (79.3) | 96.7 (82.1) |
| Hamilton Depression Rating Scale score, mean (SD) | | | |
| Total (17 items) | 15.0 (3.6) | 16.8 (4.2) | 15.8 (3.9) |
| 3 Sleep items | 3.8 (1.4) | 4.2 (1.4) | 4.0 (1.4) |
| Without sleep items (14 items) | 11.2 (3.7) | 12.3 (3.5) | 11.9 (3.6) |

Abbreviations: DDD = defined daily dose, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TAU = treatment as usual, TCA = tricyclic antidepressant.

effectiveness of brief behavioral therapy for primary insomnia.[33,34] Patients allocated to brief behavioral therapy for insomnia were asked to self-administer these skills after the termination of the intervention sessions at 4 weeks until the final assessment at 8 weeks.

Therapists for brief behavioral therapy for insomnia were 5 psychiatrists and a psychiatric nurse. All therapists had 3 or more years of clinical experience in psychiatry; however, all but one psychiatrist had not received formal cognitive-behavioral therapy training. They participated in a 2-day intensive training course on brief behavioral therapy for insomnia before the study commencement and received ongoing supervision monthly thereafter.

Treatment as usual involved having patients meet with their physician (psychiatrist) biweekly during which time they discussed their depression symptoms and obtained medication. Each session typically lasted 10 minutes. Physicians empathetically listened to patients' distress during the sessions, but changing types and doses of medication was not allowed in the first 4 weeks of the study unless rapid exacerbation of depression occurred. Physicians were allowed to discuss sleep hygiene as defined in the handout prepared for the study, but they were not permitted to discuss sleep restriction and stimulus control for insomnia.

For the assessment of integrity of both brief behavioral therapy for insomnia and TAU sessions, all sessions were audiotaped and 20% of each condition were randomly selected and evaluated by 2 independent researchers for adherence to the treatment manual or to the TAU materials.

### Data Management and Analysis

Descriptive and inferential statistics were computed using SPSS for Windows 16.0.[35] All analyses were based on the intent-to-treat model. When there were no missing data, analysis of covariance was used to test group effects while controlling for the baseline scores. When missing data were observed, linear mixed models[36] were used for continuous variables, and dropouts were assumed nonremitters for dichotomous variables. A $P$ value $< .05$ was set to test the null hypothesis. For dichotomous variables, risk ratios and their 95% confidence intervals (CIs) were calculated. A number needed to treat (NNT) was calculated when a 95% CI of risk ratio did not include 1.0.

No statistical tests were planned to detect a difference at baseline between the 2 arms because we aimed to avoid multiple tests, and the decision to adjust for baseline data in RCTs should not be determined by whether baseline differences are statistically significant.[37] However, when clinically important differences at baseline were noted from a clinician's point of view, a sensitivity analysis was performed by adjusting for all such possible confounds.

The protocol was approved by the ethics committees of all the recruiting centers. Written informed consent was obtained from all participants. The study is registered at clinicaltrials.gov (identifier: NCT00610259).

## RESULTS

### Enrollment and Baseline Characteristics of the Participants

Eighty-nine patients were screened and 37 patients satisfied the eligibility criteria, with 20 participants randomly assigned to receive the brief behavioral therapy for insomnia plus TAU therapy and 17 to the TAU therapy alone (Figure 1). Table 2 summarizes the sociodemographic and clinical