Table 1. Comparison of demographic variables between the discontinued group and the long-term use group.

Variable	Total patients (n = 140)	Discontinued (n = 64)	Long-term use (n = 76)	*p*
Age at the time of investigation (years)	53.8±10.8	53.3±10.5	54.1±11.1	ns
Age at the onset of insomnia (years)	50.8±11.0	50.3±10.9	51.3±11.0	ns
Sex (male:female)	68:72	29:35	39:37	ns
Duration of insomnia morbidity (years)	2.91±2.31	3.0±2.4	2.9±0.3	ns
Marital status (married:unmarried)	101:39	45:19	56:20	ns
Educational background (college education:not)	48:92	16:48	32:44	<0.05
Occupation (employed:unemployed)	79:61	36:28	38:38	ns
Half-life of hypnotic (ultra-short/short/intermediate/long)	(49/64/19/8)	(23/32/7/2)	(26/32/12/6)	ns
Dose of hypnotic (mg/day in diazepam equivalents)	6.0±2.2	6.1±2.2	5.9±2.1	ns
SDS score (points)	39.70±8.86	41.1±9.9	38.5±7.8	ns
PSQI total score (points)	13.6±2.0	12.3±1.8	14.8±1.4	<0.01

Values are expressed as means ±SD. The Mann-Whitney U test was used for the comparison of continuous variables between the 2 groups as follows: age, duration of insomnia morbidity, dose of hypnotics, and SDS and PSQI scores. The chi-square test was used for the comparison of categorical variables between the 2 groups as follows: sex, marital status, educational background, occupation, and half-life of hypnotic.
ns = not significant; SDS = Zung Self-Rating Depression Scale; PSQI = Pittsburgh Sleep Quality Index.
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different types of BZDs or BzRAs during the 6-month treatment period.

In the comparison of demographic variables, there were significant differences between the discontinuation group and the long-term use group regarding the educational background ($p<0.05$) and the PSQI score at the baseline ($p<0.01$). No significant differences were found between the 2 groups in terms of age at the time of the investigation, age at the self-reported onset of insomnia, duration of insomnia morbidity, SDS score, marital status, occupation, half-life of BZD or BzRA, and diazepam equivalent doses of these hypnotics (Table 1).

For all patients, the mean PSQI total score at the baseline was 13.6±2.0 points and the score at the end of the treatment period was 9.3±2.5 points. The results of comparison of PSQI total and sub-item scores between the baseline and the end of the treatment period are shown in Table 2. At the second assessment of the PSQI, the C1 (sleep quality) to the C5 (frequency of sleep disturbance) scores decreased both in the discontinuation group and the long-term use group, the C6 (use of sleeping medication) score was increased in both groups, and the C7 (daytime dysfunction) score was decreased in the discontinuation group whereas it was increased in the long-term use group. There were significant differences in the changes in the PSQI total score as well as in the C2 (sleep latency), C5 (frequency of sleep disturbance), C6 (use of sleeping medication), and C7 (daytime function) scores from the baseline to the end of the treatment period between the discontinuation group and the long-term use group (total scores, C2, C5, and C7, $p<0.01$; C6 score, $p<0.05$), whereas no significant differences in the C1 (sleep quality), C3 (sleep duration), and C4 (habitual sleep efficiency) scores between the 2 groups were found (Table 2).

Logistic regression analyses on the associated factors for the long-term use group were performed with the following 8 explanatory variables: sex, age at the self-reported onset of insomnia, age at the time of investigation, duration of the insomnia morbidity, educational background, marital status, SDS score, and PSQI total score. Among these, sex, educational background, occupation, and marital status were treated as categorical variables, and the other measured items were treated as continuous variables. As a result, multivariate analysis revealed that the long-term use of hypnotics was significantly associated only with the increase in the total PSQI score (OR = 2.8, 95% CI = 2.1–26.9, $p<0.01$) (Table 3).

We created the ROC curve to examine the cut-off PSQI total score at the baseline for predicting discontinuation of hypnotic treatment within a 6-month period. The AUC of the ROC curve was 0.86 (95% CI = 0.80–0.92). The cut-off total PSQI score at the baseline for predicting the discontinuation of hypnotic treatment within 6 months was estimated at 13.5 points; this cut-off value had a sensitivity of 0.86, a specificity of 0.75, LR+ = 3.42, and LR− = 0.19 (Figure 1).

Logistic regression analysis was conducted again to clarify the associated factors for the long-term use of hypnotics among the sub-item scores of the PSQI. Logistic regression analysis was performed with 7 sub-item scores of PSQI {sleep quality (C1), sleep latency (C2), sleep duration (C3), habitual sleep efficiency (C4), frequency of sleep disturbance (C5), use of sleeping medication (C6), and daytime dysfunction (C7)} as independent variables. The sub-item scores were treated as continuous variables. The multivariate analysis revealed that the long-term use of hypnotics for the treatment of insomnia was associated with an increase in the C1 (OR = 8.4, 95% CI = 2.4–30.0, $p<0.01$), C3 (OR = 3.6, 95% CI = 1.1–11.5, $p<0.05$), C4 (OR = 11.1, 95% CI = 3.6–33.9, $p<0.01$), and C6 (OR = 3.4, 95% CI = 1.9–6.2, $p<0.01$) scores (Table 4).

Discussion

In this study, the ratio of chronic insomnia patients who needed to continue BZD or BzRA medication for a 6-month treatment period reached more than half (54.6%) of the total number of patients enrolled in this study, which is similar to that previously reported [15]. Thus, approximately half of the patients with chronic insomnia are assumed to become long-term users of BZD or BzRA medication. As for the demographic backgrounds of the patients in this study, there were no remarkable differences in age, sex [4], duration of insomnia [15], and severity of depression [25] compared with general insomnia patients. However, the PSQI total score of the patients in this study was relatively higher than that of the insomnia patients in previous studies [26,27]. For this reason, it was speculated that patients with severe insomnia are

Table 2. Comparison of PSQI total and sub-item scores between the baseline and the end of the treatment period, and comparison of changes in these scores between the discontinued group and the long-term use group from the baseline to the end of the treatment period.

	Total patients[a] (n = 140)		Discontinued[a] (n = 64)		Long-term use[a] (n = 76)		Change in scores between the 2 time points[b]	
	Baseline	End of follow-up	Baseline	End of follow-up	Baseline	End of follow-up	Discontinued	Long-term use
PSQI total score	13.6±2.0	9.3±2.5	12.3±1.8	6.9±1.2	14.8±1.4	11.2±1.3	5.4±2.0	3.6±2.0*
C1: sleep quality	2.2±0.6	1.5±0.7	1.9±0.6	1.0±0.6	2.6±0.5	1.9±0.5	0.8±0.8	0.7±0.7
C2: sleep latency	2.5±0.6	1.1±0.5	2.6±0.6	0.9±0.3	2.4±0.5	1.3±0.5	1.6±0.7	1.1±0.7*
C3: sleep duration	2.3±0.5	1.2±0.4	2.2±0.5	1.1±0.2	2.4±0.5	1.4±0.5	1.1±0.6	1.0±0.6
C4: habitual sleep efficiency	2.1±0.6	1.4±0.6	1.8±0.6	1.0±0.3	2.4±0.5	1.8±0.6	0.8±0.6	0.7±0.8
C5: sleep disturbance	2.2±0.6	1.4±0.6	2.2±0.7	1.0±0.0	2.2±0.5	1.8±0.6	1.2±0.7	0.5±0.7
C6: use of sleeping medication	1.8±1.1	2.4±0.8	1.1±1.0	1.9±0.8	2.4±0.8	2.7±0.5	−0.8±1.3	−0.3±1.1
C7: daytime dysfunction	0.5±0.6	0.3±0.5	0.7±0.6	0.0±0.1	0.4±0.6	0.5±0.6	0.6±0.6	−0.1±0.6

[a]The Wilcoxon signed rank test was used for comparison of the scores between the 2 time points.
[b]The Mann-Whitney U test was used for comparison of the changes in these scores between the 2 groups.
Values are expressed as means ±SD for continuous variables.
*$p<0.01$;
**$p<0.05$; PSQI = Pittsburgh Sleep Quality Index.
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Table 3. Logistic regression analysis of the associated factors for the long-term use of hypnotics (n = 140).

	Univariate odds ratio (95% CI)	p	Multivariate odds ratio (95% CI)	p
Sex (male/female)		ns		ns
Age at the time of investigation (years)		ns		ns
Age at onset (years)		ns		ns
Duration of morbidity (years)		ns		ns
Marital status (married/unmarried)		ns		ns
Educational background (college educated/not)	2.2 (1.1–4.5)	<0.05		ns
Occupation (employed/unemployed)		ns		ns
Half-life of hypnotic (ultrashort/short/intermediate/long)		ns		ns
SDS score (points)		ns		ns
PSQI total score (points)	2.8 (2.0–3.99)	<0.01	2.8 (2.0–4.0)	<0.01

CI denotes confidence intervals.
ns = not significant; PSQI = Pittsburgh Sleep Quality Index; SDS = Zung Self-Rating Depression Scale.
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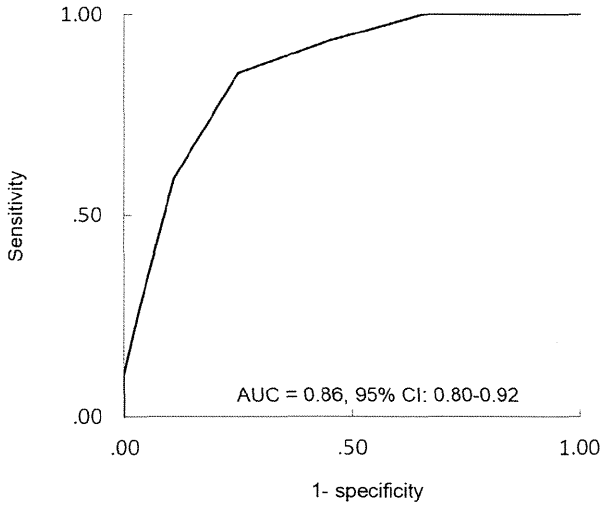
likely to visit our clinic since our clinic is a specialized and referral-based sleep disorder center. Given this fact, our results strongly indicate that it is difficult to sufficiently improve the symptoms of chronic insomnia, particularly in severe cases, with the usual dose of a single type of BZD or BzRA [28].

The results of the present logistic regression analysis showed that only the PSQI total score, not the demographic factors, appeared as the associated factor for the long-term use of the treatment. Significant relationships of female sex and older age to insomnia morbidity have been reported [4]. However, the result of the multivariate regression analysis in this study showed no significant association between long-term use of hypnotics and these demographic factors. The reason for this discrepancy is unclear. However, this result implies that there may be a difference between the factors for vulnerability to morbidity and those for responsiveness to the treatment of insomnia.



Cut-off point	Sensitivity	Specificity	LR +	LR -
11.5	1.00	0.34	1.52	-
12.5	0.93	0.55	2.06	0.12
13.5	0.86	0.75	3.42	0.19
14.5	0.59	0.89	5.43	0.46

Figure 1. Predictive cut-off point of the Pittsburgh Sleep Quality Index for the long-term use of hypnotics estimated with the receiver operating characteristic (ROC) curve. CI denotes confidence intervals. AUC = area under the curve.
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Our results showed that almost half of the patients (n = 68) had an abnormally high SDS score, although we excluded the patients affected with major depression based on the diagnostic criteria of DSM-IV-TR through the clinical interviews. However, most of them remained in the range of mild depression [19]. Thus, it seems likely that their depressive symptoms were caused secondarily by the insomnia symptom [29], although we did not evaluate the changes in depressive symptoms during the treatment period. Additionally, as shown in the results of the logistic regression analysis, the depressive symptom was not associated with the response to hypnotic treatment in this population with chronic insomnia.

The ROC curve notably revealed that the cut-off value for predicting patient discontinuation of hypnotic treatment was a PSQI score of 13.5 points at the baseline. This PSQI score was relatively higher than that of the general insomnia population at the clinical setting (average score: 8.9–10.4 points) [17,18]. Thus, although our sample population was assumed to have a sampling bias as mentioned above, our results suggest that the symptoms of patients with severe chronic insomnia having a high PSQI score are difficult to treat by a single type of BZD or BzRA at the usual dose.

Among the sub-items of the PSQI, there was a significant association of long-term use of hypnotics with C6 (sleeping medication). Considering that a high score of C6 means high frequency of hypnotic medication at the baseline in the present study, it is strongly suspected that they already had treatment resistance or tolerance to preceding BZD or BzRA medication. Interestingly, in the present study, long-term use of hypnotics showed significant association with C1 (sleep quality), C3 (sleep duration), and C4 (habitual sleep efficiency), all of which are constituents of the symptoms of sleep maintenance insomnia, whereas C2 (sleep latency), which is clearly related to sleep initiation disturbance [18], did not show statistical association with

Table 4. Logistic regression analysis of the associated factors for discontinuation of hypnotics using PSQI sub-item scores as explanatory variables.

PSQI sub-item	Univariate odds ratio (95% CI)	*p*	Multivariate odds ratio (95% CI)	*p*
C1: sleep quality	12.1 (4.9–29.5)	<0.01	8.4 (2.4–30.0)	<0.01
C2: sleep latency		ns		ns
C3: sleep duration	2.2 (1.1–4.4)	<0.05	3.6 (1.1–11.5)	<0.05
C4: habitual sleep efficiency	8.7 (3.7–20.5)	<0.01	11.1 (3.6–33.9)	<0.01
C5: sleep disturbance		ns		ns
C6: use of sleeping medication	3.9 (2.5–6.0)	<0.01	3.4 (1.9–6.2)	<0.01
C7: daytime dysfunction	0.56 (0.3–1.0)	<0.05		ns

CI denotes confidence intervals.
ns = not significant; PSQI = Pittsburgh Sleep Quality Index.
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the long-term use. In addition, the results of the logistic regression analysis showed that the half-life of BZD or BzRA was not associated with the long-term use of hypnotics. Taking these results together, sleep initiation insomnia can be substantially improved with hypnotics of any elimination half-life, as shown in previous reports [30–32]. On the other hand, sleep maintenance insomnia has been suggested to be difficult to improve only by treatment with hypnotics [33]. The results of long-term use of hypnotic treatment in patients with a higher C1 (sleep quality), C3 (sleep duration), or C4 (habitual sleep efficiency) score in the present study could support this hypothesis.

This study has several limitations. Firstly, although we showed self-reported duration of insomnia morbidity in the subject patients, we do not have sufficient information about the content, regularity, and duration of previous treatment. Secondly, because this study was conducted on patients in a single sleep disorder center, a sampling bias as indicated above should be considered. In fact, the PSQI total score in the patients examined in this study (13.6 points) was relatively higher than the score previously reported for the general insomnia population (average score: 8.9 to 10.4 points) [17,18]. Thirdly, although the treatment refractoriness was thought to be the main reason for the long-term use of BZDs or BzRAs, the other reason (dependence on drug or blind faith in the benefit of hypnotic treatment of the subject patients) should also be considered for this phenomenon. However, details about the patient's attitude about hypnotic treatment could not be obtained in the present study. Fourthly, hypnotic treatment in this study was conducted with an open and uncontrolled design, and therefore a randomized and controlled trial would be necessary in the future to investigate the factors associated with long-term use of BZDs or BzRAs in patients with chronic insomnia. Finally, although we evaluated the treatment response of patients only at the end of a 6-month treatment period, the short-term evaluation of symptoms as well as the longitudinal comparison of symptoms throughout the study period would be necessary to clarify details of the factors associated with the long-term use of BZD or BzRA hypnotics.

In conclusion, the results of this study revealed that the long-term treatment with BZD or BzRA hypnotics is associated with the severity of insomnia symptoms, and that insomnia patients whose PSQI scores are 13.5 points or higher are likely to become resistant to long-term hypnotic treatment. In addition, it appears difficult to sufficiently improve sleep maintenance insomnia with the usual dose of a single type of BZD or BzRA hypnotic. CBT has been reported to be effective for patients with chronic insomnia having hypnotic dependency [34] and has become one of the important treatment alternatives when tapering the dose of hypnotic medication in the chronic treatment of refractory insomnia [35]. To prevent the long-term use of BZD or BzRA hypnotics, adjunctive therapy with CBT should be considered for patients with treatment-resistant insomnia [13].

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Author Contributions

Conceived and designed the experiments: YT YI. Performed the experiments: YT YI. Analyzed the data: YT TK YK SA. Contributed reagents/materials/analysis tools: YT. Wrote the paper: YT.

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Modeling circadian and sleep-homeostatic effects on short-term interval timing

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Short-term interval timing i.e., perception and action relating to durations in the seconds range, has been suggested to display time-of-day as well as wake dependent fluctuations due to circadian and sleep-homeostatic changes to the rate at which an underlying pacemaker emits pulses; pertinent human data being relatively sparse and lacking in consistency however, the phenomenon remains elusive and its mechanism poorly understood. To better characterize the putative circadian and sleep-homeostatic effects on interval timing and to assess the ability of a pacemaker-based mechanism to account for the data, we measured timing performance in eighteen young healthy male subjects across two epochs of sustained wakefulness of 38.67 h each, conducted prior to (under entrained conditions) and following (under free-running conditions) a 28 h sleep-wake schedule, using the methods of duration estimation and duration production on target intervals of 10 and 40 s. Our findings of opposing oscillatory time courses across both epochs of sustained wakefulness that combine with increasing and, respectively, decreasing, saturating exponential change for the tasks of estimation and production are consistent with the hypothesis that a pacemaker emitting pulses at a rate controlled by the circadian oscillator and increasing with time awake determines human short-term interval timing; the duration-specificity of this pattern is interpreted as reflecting challenges to maintaining stable attention to the task that progressively increase with stimulus magnitude and thereby moderate the effects of pacemaker-rate changes on overt behavior.

Keywords: sleep, circadian rhythm, time perception, interval timing, mixed models

1. INTRODUCTION

Interactions between the systems underlying temporal adaptation to the geophysical cycles of the environment (e.g., by generating near-24 h rhythms in physiology and behavior) and those mediating perception and action in relation to durations in the seconds-to-minutes range (i.e., short-term interval timing), have attracted research efforts on multiple levels, involving both animal and human subjects. Whereas animal research has made considerable progress in elucidating the neurobiological correlates of these interactions and some advances on this level have been made in human research (Shurtleff et al., 1990; Soshi et al., 2010; Agostino et al., 2011a,b; Bussi et al., 2014; Golombek et al., 2014), detailed quantitative characterization on the behavioral level and interpretation with reference to relatively abstract information-processing models of the functional relationships between these timing systems remain among the central aims in the pertaining human literature.

The referenced information-processing models generally remain neutral with respect to the concrete physiological implementation of the proposed mechanisms (but see e.g., Meck, 2003; Buhusi and Meck, 2005; Wittmann, 2013 for promising efforts at integrating explanatory levels), but they are mathematically and computationally tractable and generate specific predictions that can be assessed for consistency with behavioral data. These models thus continue to present powerful explanatory and predictive devices that, beyond their practical use, provide important guidance to experimentation and theorizing (Block, 1990; Lewandowsky and Farrell, 2010).

As a consequence, a model of this type, the so-called internal clock, or pacemaker-accumulator, model of interval timing, currently dominates human research into time-of-day and wake-dependent fluctuations in short-term interval timing (Pati and Gupta, 1994; Aschoff, 1998; Nakajima et al., 1998; Miro et al., 2003; Kuriyama et al., 2005; Moore and Gunzelmann, 2013) and, while by no means the only reasonable candidate, this model has seen very good success in accounting for a broad range of timing phenomena and, in terms of general functional principles, subsumes a number of physiologically inspired mechanisms; as such, the mechanism proposed by the pacemaker-accumulator model will probably continue to be of pragmatic use into the foreseeable future.

With respect to the suggested chronobiological effects on short-term interval timing, the proposition, typically, is, that the states of the circadian oscillator and the sleep homeostat (Borbely

and Achermann, 1999) directly control the rate at which this mechanism's (Treisman, 1963) core pacemaker component emits pulses i.e., that this rate oscillates at a 24 h periodicity around an average defined by the exponential buildup and dissipation of the sleep homeostat's state across wakefulness and sleep, respectively (Pati and Gupta, 1994; Aschoff, 1998; Nakajima et al., 1998; Miro et al., 2003; Kuriyama et al., 2005; Moore and Gunzelmann, 2013).

The pulses emitted by the pacemaker, via an attention-controlled switch, reach a working memory module, or accumulator, where they are collected for comparison with the contents of a reference memory module containing pulse-duration associations acquired on previous occasions and attentional lability at the switch may introduce leakage of pulses from the system, causing a decrease in the effective number of pulses reaching the accumulator (i.e., a decrease in "effective" pacemaker-rate). A comparator component, given a criterion duration and on the basis of a continuous comparison of the contents of working memory with those of reference memory, elicits overt behavior as the number of pulses accumulated across a timing task reaches the number of pulses associated with the criterion (cf. **Figure 1**; for a detailed account of the historical development and variations of the model, see Wearden (unpublished manuscript). A multitude of a alternative models of interval timing of varied generality and level of implementation exist; for a review see e.g., Matell and Meck, 2004; for discussions regarding the putative neural substrates underlying interval timing see e.g., Meck, 2003; Matell and Meck, 2004; Buhusi and Meck, 2005; Coull et al., 2011; Wittmann, 2013).

In order to assess the plausibility of this proposed mode of interaction among timing systems, the model's predictions can be evaluated with respect to their compatibility with behavioral data; to this end, two well-established methods of human timing research lend themselves: the methods of duration estimation and duration production. In the estimation task, upon temporally delimited presentation of a stimulus, the experimental subject provides an estimate on that presentations' duration e.g., by entering a number (representing seconds of presentation) via a key-pad; conversely, in the production task, the experimental subject is presented a numeric representation of a target duration and responds e.g., by pushing a key after what he or she perceives to equal this duration.

The model, on the basis of the hypothesized circadian and sleep-homeostatic effects on pacemaker-rate, predicts specific performance changes across epochs of sustained wakefulness on each of these tasks, and a significantly improved fit (i.e., a greater improvement in fit than expected on the basis of increased model complexity alone) over the fit provided by an alternative model (such as the simple null hypothesis of no change across time) between the model's predictions and the observed data constitutes evidence in favor of the model (in analogy to the typical evaluation of e.g., simple linear regression or ANOVA models Estes, 1991; Maxwell and Delaney, 2003; Judd et al., 2008; Lewandowsky and Farrell, 2010).

For the *production* task, specifically, a relative increase in pacemaker-rate implies that the number of pulses corresponding (according to reference memory) to the requested duration

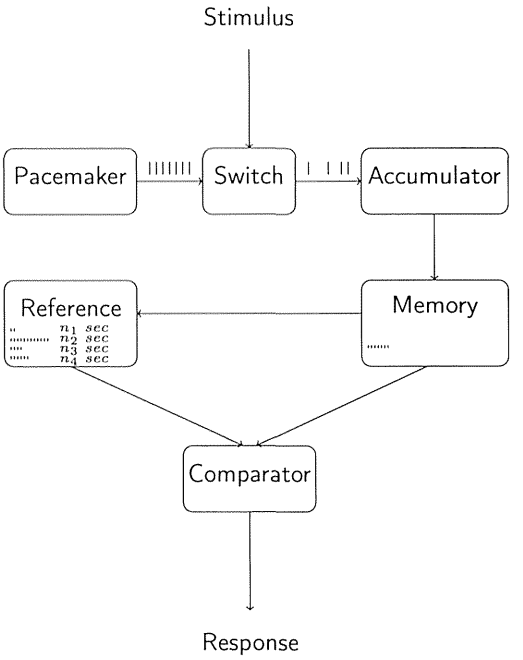

FIGURE 1 | Outline of the internal clock model of interval timing. The pacemaker emits pulses at a rate that depends on organismic state and is hypothesized to be under the control of circadian and sleep-homeostatic processes. Pulses are gated into the accumulator and working memory components via an attention-controlled switch and attentional lability may lead to a leakage of pulses at this stage. The comparison of working memory contents with a reference memory containing pulse-duration associations formed during previous experiences constitutes the basis for overt behavior. Adapted from Wearden (unpublished manuscript).

is accumulated in a shorter amount of time and thus leads to a relative decrease in produced duration i.e., the relationship between pacemaker-rate and produced duration is reciprocal. Conversely, for the task of *estimation*, the number of pulses accumulated across the duration of stimulus presentation increases accordingly, and a relative increase in pacemaker-rate thus entails an increase in duration estimates. Analogous reasoning, naturally, extends to the case of a linear depression in pacemaker-rate, as well as to the more complex patterns of change in pacemaker-rate specified by the proposed circadian and sleep-homeostatic effects.

Accordingly, as a direct consequence of the model's design, a pacemaker-rate that oscillates at a 24 h periodicity (effect of the circadian oscillator) around an exponentially changing average (effect of changes to sleep-homeostat state), will entail a corresponding pattern in estimation performance and a reciprocal pattern in production performance, and this pattern, when expressed relative to stimulus duration (i.e., as the ratio *response/stimulus*), does not depend on stimulus magnitude.

If the assumption is made, however, that timing of shorter vs. longer durations differs in that maintaining stable attention to a stimulus becomes increasingly challenging with stimulus duration (Taatgen et al., 2007), the observed patterns for unequal stimulus magnitudes should diverge, leading to differing parameter

values of the exponential and sinusoidal components in predicted behavior. More specifically, because, under this assumption, the number of pulses leaking from the system is assumed to be disproportionately greater for longer durations, the relative effect of a given increase in pacemaker-rate is smaller for the estimation of longer durations than it is for the estimation of shorter durations and thus leads to a widening gap across time between estimation trajectories for unequal durations; conversely, due to the *reciprocal* relationship between pacemaker-rate and *produced* duration, the model predicts a convergence across time of production levels for unequal durations.

Analogous reasoning naturally extends to the hypothesized compound exponential and sinusoid pattern characterizing the temporal development of pacemaker-rate and beyond that, circadian and sleep-homeostatic modulations to attentional lability could entail even more complex deviations from the identity pattern predicted if attention played no substantial role.

In reality, evaluation of the proposition, that circadian and sleep-homeostatic effects act in the above-specified manner on the mechanism to generate behavioral fluctuations, has proven rather difficult, as the pertinent human data is relatively sparse and lacking in consistency.

The reports on supportive evidence cited above are not free of methodological problems and are pitted against a number of studies relating negative or ambiguous results (Esposito et al., 2007; Späti, 2011; Pande et al., 2014), a situation that, according to some authors can, in part, be attributed to methodological and terminological incompatibilities across studies (Pande and Pati, 2010; Späti, 2011; Miguel, 2012; Moore and Gunzelmann, 2013). The prevalence of study designs that employ only singular timing methods and stimulus durations, the heterogeneity of instructions to subjects regarding the timing strategy to adopt and under-powered analytical approaches don't make optimal use of resources and further limit comparability of results.

As a consequence, we still lack clarity regarding the exact functional form of the suggested interaction and how it depends on task and stimulus duration, making evaluation of the proposed mechanism and the relative susceptibility of its components to circadian, sleep-homeostatic and, potentially, attentional, challenges difficult.

Here, in an effort to improve upon a number of these shortcomings, we aim at characterizing the conjectured chronobiological effects on interval timing by employing the methods of duration estimation and duration production on different target intervals within a unified experimental setting and, as a consequence, accumulate more reliable evidence regarding the proposed interaction between chronobiological and interval timing systems.

We chose to assess timing of two target durations via the tasks of duration estimation and duration production across two epochs of sustained wakefulness carried out within a constant routine setting under entrained (i.e., subjects' biological rhythms are synchronized with environmental cycles) and, respectively, free-running conditions (i.e., subject's biological rhythms are decoupled from environmental cycles and run at their individual, intrinsic near-24 h, circadian, periodicities).

Following the theoretical considerations outlined above, we assumed both tasks to be reasonably characterized by a 24 h-oscillation around an average that follows a saturating exponential with time constant 18.2 h (Borbely and Achermann, 1999; Van Dongen et al., 2007, 2012) i.e., to follow a function of the form $Y_i = S_i + C_i + \epsilon_i$, where i is used to distinguish between individual subjects' curves across time i.e., between subjects' individual timing trajectories, S represents a saturating exponential component reflecting state of the sleep homeostat, C represents a sinusoid term reflecting state of the circadian oscillator and ϵ represents the deviations of the observed data points for subject i from the true subject-specific trajectory.

Trajectories are expected to vary in their parameters across subjects around averages defined by specific combinations of task, stimulus duration and constant routine i.e., by eventual significant simple and interactive effects of the factors under scrutiny and, following from the hypothesized endogenous character of the circadian and sleep-homeostatic effects, the pattern, when expressed relative to the endogenous rhythmicity in melatonin, is expected to remain stable across entrained vs. free-running conditions.

In summary, the theoretically motivated algebraic form chosen to characterize behavior across time in the individual can be compared with alternative forms (constant, sinusoid only, exponential only, sinusoid plus exponential, different vs. equal exponentials across durations, etc.) representing alternative hypotheses regarding simple and interactive effects of circadian phase, state of the sleep homeostat, etc. and, via embedding in an appropriately developed hierarchical structure, can readily accommodate the hypothesized effects of further factors and account for the expected variation in subjects' idiosyncratic trajectories.

2. METHODS

Data on the production and estimation of 10 and 40 s was obtained from eighteen healthy young male subjects sampled at 2 h-intervals across two constant routine (CR) epochs conducted under conditions of sustained wakefulness (SD) of 38.67 h each, which were separated by an intervening 7 day-epoch of forced desynchrony (FD; cf. **Figure 2**).

2.1. SUBJECTS

Eighteen young male subjects aged 19–39 years (mean ± sd: 22.44 ± 4.33 y) without any known sleep, physical, or psychiatric disorders or any history of using psychoactive drugs, as confirmed via a semi-structured interview conducted by a psychiatrist, all-night clinical polysomnography, blood chemistry tests, and several screening questionnaires, participated in the study; measures obtained from seventeen of these subjects have been previously published in entirely different contexts (Hida et al., 2013; Kitamura et al., 2013). None of the subjects had worked night shifts or traveled across time zones within 6 months preceding the study; none of the participants displayed clinical signs of visual impairment and fundus examination detected no morphologic abnormalities of the retina. The study design was approved by the local ethics committee and all participants gave their informed consent; all procedures conformed to the Declaration of Helsinki.

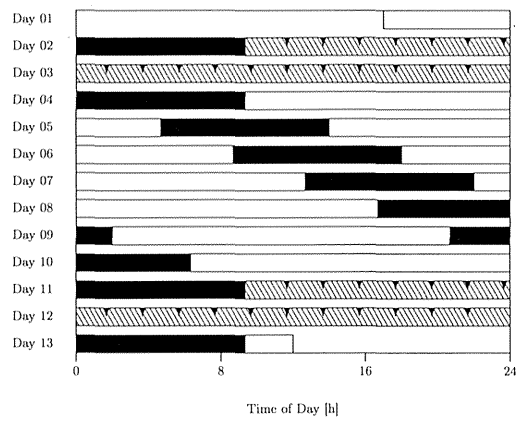

FIGURE 2 | Forced desynchrony (FD) protocol. Filled bars, scheduled sleep (0 lx); open bars, wakefulness in dim light (15 lx); hatched bars, constant routine (CR). The FD protocol used in this study was a 28-h sleep–wake cycle consisting of alternating epochs of 9.33 h of sleep and 18.67 h of wakefulness. Interval timing tasks were administered at two-hourly intervals throughout both CRs (Days 2–3; Days 11–12; reported here; arrows indicate sampling points) as well as across the central part of the FD protocol (evening of Day 7 to afternoon of Day 8; not reported here).

2.2. PROTOCOL

Subjects underwent a 13-day protocol in a temporal isolation laboratory devoid of external time cues (previously described in Kitamura et al., 2013). Briefly, participants entered the laboratory at 5 P.M. on Day 1 and, after having a meal and taking a bath, turned the lights off and went to bed at 12 A.M. The protocol, which started the following morning after 9.33 h of bed rest, comprised measurement of melatonin rhythm and interval timing under constant routine conditions (CR1) followed by a 28 h sleep-wake schedule for 7 days, and a second measurement of melatonin rhythm and interval timing under constant routine conditions (CR2).

The intervening 28 h sleep-wake schedule consisted of alternating cycles of 9.33 h of scheduled sleep (promoting sleep/bed-rest with lights off) and 18.67 h of scheduled wakefulness (prohibiting sleep). Throughout the study, subjects were under constant surveillance by a researcher and were verbally awakened when they unintentionally fell asleep during the wake period. Subjects were asked to maintain a semi-recumbent posture under low-intensity light conditions (< 15 lx) and consume small meals (approx. 200 kcal) at 2-h intervals; water was the only source of liquid intake and was available *ad libitum* (no other beverages, including coffee or any other alertness-boosting beverages were allowed). During wake periods, participants were allowed to move freely around the laboratory, read and write, enjoy music and videos, play video-games, and engage in conversation with the researcher. During scheduled sleep, subjects were asked to sleep in the bedroom with lights off (0 lx).

2.3. MEASURES

2.3.1. Melatonin

During each 38.67 h-epoch of sustained wakefulness, blood samples were collected at 60 min intervals via a stopcock attached directly to an intravenous catheter and centrifuged; the plasma collected was frozen at −80°C for radioimmunoassay of melatonin concentrations.

2.3.2. Interval timing

In order to trace the relationship between objective and subjectively perceived duration across the study protocol, we used two methods classically employed in human interval timing research i.e., the methods of estimation and production (Clausen, 1950; Bindra and Waksberg, 1956; Wallace and Rabin, 1960), which were implemented using the `E-Prime` stimulus presentation software (version 1.1.4.6) on a laptop computer.

In the estimation task, upon temporally delimited presentation of a stimulus (filled red circle on white background, centered on the display of the laptop computer), the participant provided an estimate on that presentations' duration by entering a number (representing seconds of presentation) via a key-pad. In the production task, the participant was presented a numeric representation of a target duration (white number on blue background, centered on the display of the laptop computer and representing duration in seconds to produce) and pushed a key after what he perceived to equal this duration. In each interval timing session all subjects performed temporal estimation and production of 10 and 40 s. At each measurement occasion, each stimulus/task combination was given three times in randomized sequence, each measurement occasion lasting approx. 7 min.

2.4. ANALYSIS

2.4.1. Melatonin

Plasma melatonin concentrations were measured using a radioimmunoassay (RIA) technique (SRL, Tokyo, Japan) at an assay sensitivity of 2.8 pg/ml. DLMO (dim light melatonin onset) was defined as the time of a cosine-fitted curve, when plasma melatonin concentrations rose from a low background level to above 10 pg/ml (24/12-h composite cosine model fitted to the z-score standardized data using `ChronoLab 3.0`).

2.4.2. Interval timing

Estimation and production data was analyzed using a random coefficient model in `R`'s (version 3.1; R Core Team, 2014) `nlme` (Pinheiro et al., 2015) package.

The ratios of the subject's average response to the target (stimulus-) duration at each measurement occasion, multiplied by 100 for computational reasons, served as the source to further analyses. Values of this measure above one hundred thus denote over(estimation/production) and values of this ratio below one hundred denote under(estimation/production); a value of one hundred for this ratio implies exact, veridical, estimation/production. Outcome values were removed from the dataset prior to analysis if their standardized value was ≥ 250.

The following predictors were used as fixed factors: task (production, estimation; TASK), stimulus (10, 40 s; STIM), constant routine (CR1, CR2; CR) and time relative to DLMO.

In the model building process, we included the exponential function $\exp(-t/18.2)$, representing state of the sleep homeostat across sustained wakefulness (Borbely and Achermann, 1999;

Van Dongen et al., 2007, 2012) as well the predictors sin $(2\pi/24\,t)$ and cos $(2\pi/24\,t)$, jointly representing state of the circadian oscillator (due to the equivalence $A \cdot \cos(\omega t - P) = s \cdot \sin(\omega t) + c \cdot \cos(\omega t)$) for time.

Theoretically motivated interactive terms were included if they improved model fit, which was evaluated using likelihood ratio tests; we included a random intercept and random slopes for stimulus and task as this improved model fit; also, the model fitted different variances by tasks and stimuli due to variance heterogeneity among groups.

The model developed was:

$$
\begin{aligned}
y_{ij} &= \beta_0 + \beta_1 TASK_{ij} + \beta_2 STIM_{ij} + \beta_3 CR_{ij} \\
&+ \beta_4 \exp(-t_{ij}/18.2) + \beta_5 \sin(2\pi/24 t_{ij}) + \beta_6 \cos(2\pi/24 t_{ij}) \\
&+ \beta_7 TASK_{ij} \times STIM_{ij} + \beta_8 TASK_{ij} \times CR_{ij} \\
&+ \beta_9 TASK_{ij} \times \exp(-t_{ij}/18.2) + \beta_{10} TASK_{ij} \times \sin(2\pi/24 t_{ij}) \\
&+ \beta_{11} TASK_{ij} \times \cos(2\pi/24 t_{ij}) + \beta_{12} STIM_{ij} \times \exp(-t_{ij}/18.2) \\
&+ \beta_{13} STIM_{ij} \times \sin(2\pi/24 t_{ij}) + \beta_{14} STIM_{ij} \times \cos(2\pi/24 t_{ij}) \\
&+ b_{0i} + b_{1i} TASK_{ij} + b_{2i} STIM_{ij} + \epsilon_{ij}
\end{aligned}
$$

where i = subject, j = time point, y_{ij} = response (produced, estimated duration), $STIM_{ij}$ = stimulus duration (10, 40 s), CR_{ij} = constant routine (CR1, CR2), $TASK_{ij}$ = task (estimation, production), t_{ij} = time from DLMO in hours, β_1 to β_{14} = regression coefficients of the independent variables, b_{0i} = subject-specific random intercept and, b_{1i} and b_{2i} = subject-specific random slopes for task and stimulus, respectively.

3. FINDINGS

Consistent with our hypothesis of circadian and sleep-homeostatic control of an internal clock model's pacemaker rate, estimation and production of two target durations is readily accommodated by a random coefficient-model for both tasks that comprises a saturating exponential term as well as simple trigonometric terms relating duration production and estimation to states of the sleep homeostat and the circadian oscillator.

Trajectories of duration estimation and production, during each epoch of sustained wakefulness, displayed a relatively large degree of inter-individual variability, both in terms of unconditional levels and in terms of effects of task and target duration on these levels, as indicated by the fact that inclusion of a random intercept and random slopes for stimulus and task significantly improved model fit (cf. **Figure 3**), which may suggest subject-specific variation in baseline arousal and attentional level as well as potentially differing timing strategies.

The sinusoidal component of the response to target-ratio's trajectory (main effect sin $(2\pi/24t)$), on average, varied across the two tasks of estimation and production (interaction sin $(2\pi/24t) \times TASK$) as well as across the target intervals of 10 and 40 s (interactions $STIM \times \sin(2\pi/24t)$ and $STIM \times \cos(2\pi/24t)$); the exponential component of the response-to-target ratio's trajectory, across subjects and averaged across the tasks of estimation and production, was more positive for the 10 s stimulus (overall trend positive), than for the 40 s stimulus (overall trend negative; interaction $STIM \times \exp(-t/18.2)$). The ratio was typically below one for estimation (underestimation) but increased over time to reach values close to one, whereas it began above one for production (overproduction) to decrease over time and finally reach values below one (under-production; interaction $\exp(-t/18.2) \times TASK$) (cf. **Table 1** and **Figure 4**).

This pattern is consistent with a wake-dependent increase in addition to a circadian oscillation in the rate at which the underlying pacemaker emits pulses as this, as outlined in the introduction, entails a corresponding pattern in estimation and a reciprocal pattern in production.

The variation in the expression of the pattern in function of stimulus duration further suggests an interaction of change

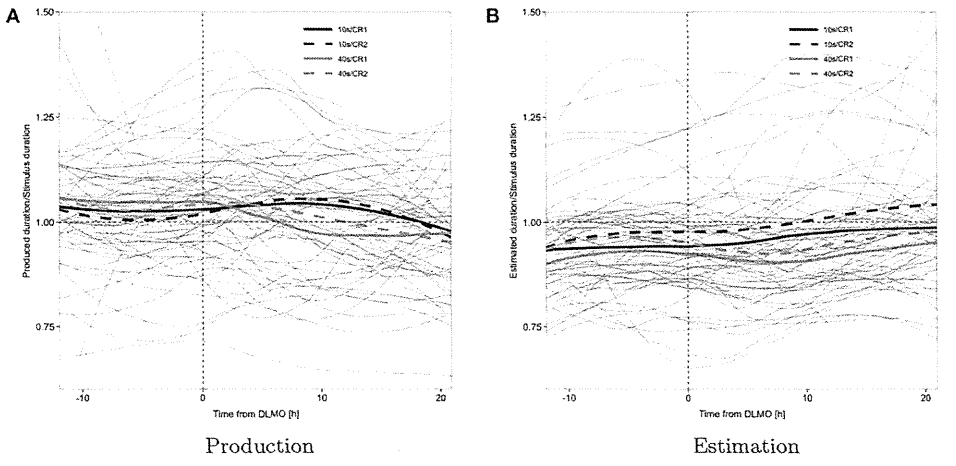

FIGURE 3 | Observed data; individual subject's loess smoothed trajectories (thin solid gray lines; one trajectory per subject and condition) and average time course across all subjects by target duration and constant routine (thick; black, 10 s; gray, 40 s; solid, CR1; dashed, CR2); the horizontal reference line represents veridical timing; the vertical reference line represents dim light melatonin onset (DLMO).

in pacemaker rate with attentional factors in determining overt behavior: specifically, the more positive exponential component for the trajectory of 10 s, when compared to that for 40 s (reflected in a steeper increase in estimation and shallower decrease in production associated with this duration), suggests that duration-specific attentional demands moderate the effects of changes in pacemaker-rate on overt timing behavior ($STIM \times \exp(-t/18.2)$), thus leading to unequal "effective" pacemaker rates (i.e., the actual rates at which pulses reach the accumulator) across durations; the observed pattern is consistent with a pulse loss at the attention-gated switch that progressively increases with target duration and may reflect an increase in attentional lability with target duration (Taatgen et al., 2007). As a consequence, a given increase in pacemaker rate has relatively less effect on the increase in estimation for longer durations than it does for shorter durations, leading to a widening gap between the exponential components in estimation. Due to the reciprocal relationship between pacemaker rate and production, we observe a convergence for production, and analogous reasoning extends to duration-specific characteristic of the sinusoidal terms.

Table 1 | Estimated coefficient by model term.

Effect	Value	Std.Error	DF	*t*-value	*p*-value
(Intercept)	102.13	2.32	2424	43.95	0.00
CR	0.19	0.79	2424	0.23	0.81
STIM	−4.72	1.72	2424	−2.75	0.01
$\exp(-t/18.2)$	2.24	3.23	2424	0.69	0.49
$\sin(2\pi/24t)$	2.64	0.68	2424	3.86	0.00
$\cos(2\pi/24t)$	−0.92	0.68	2424	−1.36	0.17
TASK	−2.38	4.83	2424	−0.49	0.62
CR × *TASK*	2.66	1.06	2424	2.51	0.01
STIM × *TASK*	−2.84	1.08	2424	−2.62	0.01
$\exp(-t/18.2) \times$ *TASK*	−17.19	3.56	2424	−4.83	0.00
$\sin(2\pi/24t) \times$ *TASK*	−3.28	0.75	2424	−4.38	0.00
$\cos(2\pi/24t) \times$ *TASK*	−0.63	0.74	2424	−0.86	0.39
STIM × $\exp(-t/18.2)$	13.29	3.58	2424	3.71	0.00
STIM × $\sin(2\pi/24t)$	−2.05	0.76	2424	−2.69	0.01
STIM × $\cos(2\pi/24t)$	2.20	0.75	2424	2.94	0.00

This interpretation is further supported by the observation of unequal amplitudes in the oscillatory component for short vs. long durations ($STIM \times \sin(2\pi/24t)$); the observed phase difference in oscillation across durations ($STIM \times \cos(2\pi/24t)$) may however suggest additional circadian and/or sleep-homeostatic effects on attention (over and above the respective effects on pacemaker-rate).

The ratio was higher for the 10 s than for the 40 s stimulus and during CR2 vs. CR1 in estimation, whereas no corresponding differences were observed in production (interactions *STIM* × *TASK*, *CR* × *TASK*) a finding that, again, may be accounted for by the fact that the internal clock model directly relates estimation to pacemaker-rate but specifies a reciprocal relationship between pacemaker-rate and production and thus leads to different behavioral consequences of changes in pacemaker-rate across tasks (*STIM* × *TASK*).

Again, as outlined above, an increasing pacemaker rate, combined with differential pulse loss due to attentional fluctuations across durations, leads to different rates of increase in the response across durations, thus accounting for the widening gap evident in estimation ratios across different durations; conversely produced duration-ratios across targets progressively converge.

In combination with a hypothesized greater attentional stability during the second constant routine, which may be attributed to the effect of habituation to the task, the unequal relationship between estimated and produced durations to pacemaker-rate may also account for the significant increase in level across constant routines observed for estimation that is absent from production (*CR* × *TASK*): a relative increase in "effective" pacemaker-rate across constant routines, due to the direct relationship, is bound to affect overall levels of the response more strongly for the task of estimation and thus lead to the observed difference in effects across the tasks of estimation and production.

4. DISCUSSION AND OUTLOOK

Our observations and interpretation are generally in line with the results reported in Späti (2011) but reveal the more appropriate

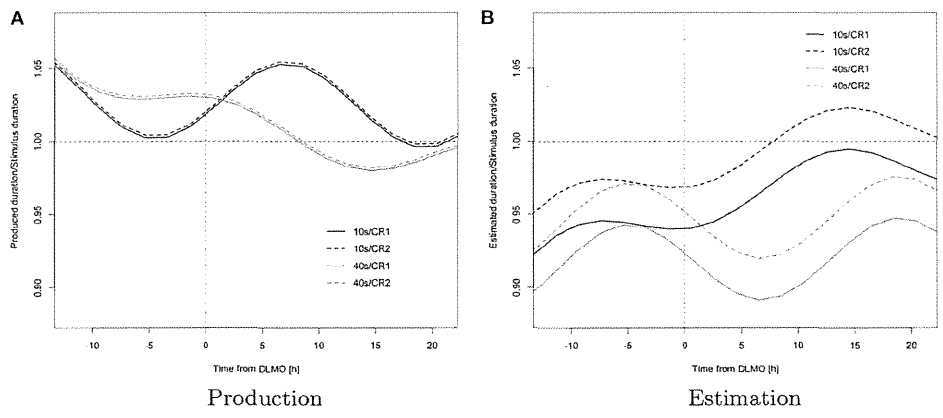

FIGURE 4 | Model predictions; black, 10 s; gray, 40 s; solid, CR1; dashed, CR2; the horizontal reference line represents veridical timing; the vertical reference line represents dim light melatonin onset (DLMO).

design of our study which allows for testing of specific hypotheses, including the more adequate nature of a random coefficient modeling approach to evaluation of this kind of data: the repeated measures analysis of variance approach to assessing production and reproduction trajectories collected under sustained wakefulness used in Späti (2011) identified the dependence of trajectories on task and stimulus magnitude but, possibly due to a lack in statistical power, failed to determine the circadian and wake-dependent modulations in production suggested by visual inspection; here, on the other hand, using a random coefficient-modeling approach to the analysis of chronobiological time series, we were able to suggest and test the exact way in which interval timing trajectories are affected by the interaction of circadian and homeostatic effects with stimulus magnitude and nature of the task and, as a consequence, test more specific hypotheses (for recent, accessible overviews on some of the shortcomings of more traditional approaches to the analysis of longitudinal data and how these are addressed by random coefficient modeling, see Winter, 2013; Finch et al., 2014; Mirman, 2014 as well as the more thorough treatments in Singer and Willett, 2003, Pinheiro and Bates, 2009 and Long, 2011; for application to a chronobiological context in R and, respectively, SAS, see Seltman, 1997; Albert and Hunsberger, 2005; for further examples on the use of R in a chronobiological context, see Barnett and Dobson, 2010, as well as Lee Gierke et al., 2013, Qiu et al., 2014 and Sachs, 2014).

Further comparison with the pertinent literature, corroborate a picture drawn by our data that is largely consistent with previous findings but of much greater detail and thus more theoretically informative: Nakajima et al., in a 36 h-sleep deprivation study on four healthy young men involving production of 10 and 60 s, observed an oscillatory pattern in responses with minimal production of 10 s around 10 P.M. and minimal production of 60 s around 7 P.M., a pattern that is consistent with the general trends observed for production, for our data (Nakajima et al., 1998). Also in line with our findings are results reported by Kuriyama et al. who, during 30 h of sustained wakefulness involving 8 subjects, reported an oscillatory pattern with a minimum in the evening (17–21 h) for the production of 10 s (Kuriyama et al., 2005).

As was the case for the study reported here, Kuriyama et al. explicitly discouraged subjects from counting and rhythmisizing; as it remains unclear however, what instructions were given to subjects on this issue in the study reported by Nakajima et al., comparisons with this experiment need to be understood with caution.

In the studies mentioned below, on the other hand, subjects were either instructed to count and rhythmisize or the design employed was very different from the one used in our study in a number of other aspects; these studies are thus reported here primarily to illustrate the heterogeneity of methodologies and findings and, as a consequence, comparisons with the data reported here are rather difficult to draw.

Soshi et al., after one night of sustained wakefulness involving 18 subjects in a pre/post comparison (21:00–09:00), found a decrease in the production of 10 s (but an increase under conditions of sleep satiation) (Soshi et al., 2010) and Aschoff, in production of 5 and 10 s by seven subjects, reported an anti-cyclical oscillation to core body temperature but no association with wake time (Aschoff, 1998).

In contrast, Pati and Gupta in 10 subjects, under everyday conditions and employing a counting strategy, reported a parallel oscillation of 10 s production with core body temperature (Pati and Gupta, 1994) and Esposito et al., using a 15-s rhythmisizing task on 54 subjects across one night of sustained wakefulness found neither circadian nor sleep-homeostatic effects (Esposito et al., 2007).

On the other hand, Miro et al., using 10 s production under a counting paradigm across 60 h of sustained wakefulness, reported circadian minima occurring around 17–21 h that combined with a linearly increasing component across the protocol (Miro et al., 2003).

This heterogeneity in findings and the contrast with our results, again, stresses the importance of careful distinction between designs. A limitation with our study shared with those carried out by other groups is the relatively poor control on the strategies adopted by individual subjects. In some of the aforementioned studies, the authors encouraged counting or sequencing strategies, while other reports give no information about the exact instructions given and/or compliance with them. In our study, counting or sequencing were explicitly discouraged but compliance is difficult to control and, possibly, also difficult to expect in the tasks of production and estimation, where durations are actually given/requested numerically. A simple suggestion for improvement that circumvents the introduction of distractor tasks, is the use of *post-hoc* questionnaires to be completed after each timing session which provide the participants with a means to self-evaluate their performance with respect to the strategies employed and that can be accounted for in the data analytic process.

In summary, while generally in line with previous reports on the circadian and sleep-homeostatic modulation of interval timing, our results, by combining assessment of production and estimation of two stimulus magnitudes across sustained wakefulness under entrained and free-running conditions with the more powerful approach of random coefficient modeling to data analysis, draw a much more detailed picture and allow for more specific and robust inferences regarding the putative operation of the hypothesized pacemaker-accumulator mechanism, the adequacy of which in accounting for critical features of the data we could confirm and, concurrently refine: whereas our findings are consistent with the hypothesis of circadian and sleep-homeostatic modulations in the rate of an underlying pacemaker and suggest that its pulse rate oscillates at a 24 h-period around an increasing saturating exponential with time constant 18.2 h, our results also point at an important role of attentional demands in timing a given duration, by moderating the impact of pacemaker rate on observed behavior; changes in pacemaker rate alone cannot explain the full complexity of the observed pattern.

Further evaluation of interactions between the timing systems studied in chronobiology one the one hand and cognitive psychology and psychophysics on the other hand should profit from an extension of our approach encompassing tasks that avoid translation to and from explicit numerical representations, from careful control on subjects' strategies as well from the

use of different target intervals in order to assess the limits to which the model can accommodate the data. Chronobiological interventions in concert with measures aimed at further separating the relative contribution of attentional factors from those related to pacemaker rate, such as concurrent assessment of physiological and psychological parameters, should support further theorizing. Future research should be directed at whether more physiologically informed models can account for the data, as well as at what role e.g., modulation in dopaminergic pathways (Buhusi and Meck, 2005; Bussi et al., 2014; Wearden, unpublished manuscript) may play in accounting for the behavior observed (dopaminergic transmission has been shown to be relevant in the circadian modulation of interval timing and to be associated with pacemaker-rate in the internal clock model as well as with frequency and synchronization of cortical oscillations and resetting of the membrane properties of striatal spiny neurons on stimulus onset in the physiologically informed striatal beat frequency model Matell and Meck, 2004; Buhusi and Meck, 2005; Meck et al., 2008). Finally, concurrent measurement of higher-order timing faculties may provide valuable insights into human timing beyond the relatively narrow limits studied here and help elucidate as of yet poorly understood phenomena such as cognitive temporal orientation (Späti et al., 2009) (but see Wackermann, 2014 for a discussion of caveats regarding unreflected generalization of concepts across domains).

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ORIGINAL RESEARCH

The burden of insomnia in Japan

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Objectives: Several studies have suggested that patients who experience insomnia report a number of significant impairments. However, despite this literature, fewer studies have focused on the burden of insomnia among patients in Japan. The objective of the current study is to extend this work in Japan to further understand the effect of insomnia on health-related quality of life (hrQOL). Further, another objective is to understand general predictors of hrQOL among patients with insomnia.

Methods: Data from the 2012 Japan National Health and Wellness Survey, an annual, cross-sectional study of adults aged 18 years or older, were used (N=30,000). All National Health and Wellness Survey respondents were categorized based on the incidence of self-reported insomnia diagnosis and prescription medication usage (clinical insomniacs under treatment versus [vs] good sleepers without insomnia or insomnia symptoms). Comparisons among different groups were made using multiple regression models controlling for demographics and health history.

Results: Clinical insomniacs (n=1,018; 3.4%) reported significantly worse hrQOL compared with good sleepers (n=20,542) (mental component summary: 34.2 vs 48.0; physical component summary: 48.0 vs 52.8; health utilities: 0.61 vs 0.76; all $P<0.05$). Health behaviors (smoking, exercise, alcohol use) and comorbidities were the strongest predictors of health utilities for clinical insomniacs. For all three clinical insomniac subgroups of interest, those with a physical comorbidity but not a psychiatric one, those with a psychiatric comorbidity but not a physical one, and those without either a physical or psychiatric comorbidity, large decrements in health utilities were observed for respondents who did not engage in any positive health behaviors (0.61, 0.57, 0.64, respectively) relative to good sleepers (0.78). However, the gap in health utility scores between these subgroups and good sleepers diminishes with an increasing number of positive health behaviors (eg, clinical insomniacs with a physical comorbidity but not a psychiatric comorbidity performing all three positive health behaviors =0.67 vs good sleepers =0.78).

Discussion: A significant burden remains for those with insomnia who are treated. Given the particularly low levels of hrQOL among treated insomnia patients who have poor health behavior profiles and have psychiatric comorbidities, physicians should place particular emphasis on these patients who are most in need of intervention. Improved treatments may help to address the unmet needs of these patient populations.

Keywords: insomnia, quality of life, health behaviors

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Introduction

Although its prevalence varies considerably by the definition used,[1–8] insomnia is a serious condition with wide-ranging effects. Primary insomnia, as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, Text Revision and the International Classification of Sleep Disorders, second edition by the American

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Academy of Sleep Medicine, is observed in approximately 6% of adults.[2,3] However, symptoms of insomnia are quite common across the life cycle.[8–10] For example, difficulty initiating sleep, difficulty maintaining sleep, and early morning awakening have been experienced in the past month by approximately 30% of the adult population.[1,4,9,11]

The presence of insomnia has been associated with increased anxiety and depression,[12] impaired quality of life,[12] and greater indirect and direct societal costs.[13–17] Bolge et al used data from the 2005 United States National Health and Wellness Survey (NHWS) and found that respondents who had been diagnosed with insomnia and experienced their symptoms at least a few times per month reported significantly worse health-related quality of life (hrQOL), more missed work (absenteeism), more impairment while at work (presenteeism), and greater impairment in leisure activities.[18] Indeed, a recent systematic review of 58 studies found a consistent effect of insomnia symptoms on social and work-related functioning, cognition and mood, and overall health care burden.[19]

However, despite this literature, fewer studies have focused on the burden of insomnia among patients in Japan. One exception is a recent study conducted by Sasai et al which categorized patients into "good sleepers" using and not using sleep medication and patients with insomnia using and not using sleep medication based on Pittsburgh Sleep Quality Index scores.[20] The results suggested a significant physical and mental burden of insomnia for patients with insomnia in Japan and also suggested a further physical burden (but not a mental one) for those using medication, possibly due to the side effect profile of the medications.

The objective of the current study is to extend this work in Japan to further understand the effect of insomnia on hrQOL. More specifically, the analyses presented will examine the differences in health outcomes among those with insomnia and who are treated compared with those without insomnia or symptoms of insomnia. Further, another objective is to determine predictors of hrQOL among those who are using a medication for their insomnia to aid clinicians in the identification of potentially modifiable factors which can benefit the daily functioning of patients.

Methods

Data source

The current study used data from the 2012 Japan NHWS (Kantar Health, New York, NY, USA), an annual, cross-sectional study of adults aged 18 years or older (N=30,000). The NHWS is a general health survey which includes questions on medical conditions, symptoms, treatment information, and health outcomes among other variables. The survey is completed online and potential respondents to the NHWS are recruited through an existing Internet panel. The members of this panel are recruited through a variety of methods (eg, newsletters, online banner advertisements, etc). However, to minimize sampling bias, the NHWS recruited members of this panel using a stratified random sample framework (with quotas based on sex and age) to match the characteristics of the adult population in Japan. Comparisons between the Japan NHWS and governmental sources are reported elsewhere.

All respondents provided informed consent and the study protocol was reviewed and approved by an Institutional Review Board.

Sample

All respondents from the Japan NHWS were included in the analyses (N=30,000).

Measures

Insomnia symptoms

All respondents of the NHWS were asked whether they had insomnia or sleep difficulties (and, if so, whether those conditions had been diagnosed). All respondents were also presented with a list of sleep-related symptoms and asked to select which ones they regularly experience. These symptoms included "difficulty falling asleep", "waking during the night and not being able to get back to sleep", "poor quality of sleep", "waking up several times during the night", and "waking up too early".

Also, all respondents who reported they are experiencing insomnia or reported experiencing insomnia symptoms also indicated whether or not they are taking a medication for their condition. The specific medication was also reported by the respondent.

From these data, two groups were created to quantify the burden of insomnia: those who reported having been diagnosed with insomnia and using a prescription medication (clinical insomniacs) and those who did not report having insomnia or having symptoms associated with insomnia (good sleepers). We focused on clinical insomniacs to avoid including patients with a sub-clinical level of insomnia or those who were improperly managed (ie, above a clinical threshold for insomnia but not receiving adequate treatment).

Demographics

Demographic variables included sex, age, education (less than university graduate versus [vs] university graduate),

annual household income (<¥3 million [MM], ¥3 MM to <¥5 MM, ¥5 MM to <¥8 MM, ¥8 MM or more, or decline to provide income), and employment status (currently employed, unemployed but looking for work [including those who are on disability], or unemployed but not looking for work [including those who are retired or homemakers]).

Health history

Smoking status ("do you currently smoke cigarettes?"; coded as current smoker ["yes"/"yes, but I'm trying to quit"] vs current non-smoker ["never smoked"/"no, I quit"/"no, I'm in the process of quitting"]), exercise behavior ("how many days in the past month did you exercise vigorously for at least 20 minutes?"; coded as exercised in the past month [1 day or more] vs did not exercise in the past month [0 days]), alcohol use ("how often do you drink alcohol?"; coded as currently drink alcohol ["daily"/"4–6 times per week"/"2–3 times per week"/"once a week"/"2–3 times per month"/"once a month or less"] vs do not currently drink alcohol ["I do not drink alcohol"]), and body mass index. Physical comorbidities were assessed using the Charlson comorbidity index (CCI) which represents an index score summarizing the overall comorbidity burden of each respondent. The CCI is calculated by weighting the presence of severe comorbidities and summing the result.[21] Patients who reported experiencing either anxiety or depression were considered to have a psychiatric comorbidity.

hrQOL

hrQOL was assessed using the physical component summary (PCS) and mental component summary (MCS) scores from the Short Form-36 version 2 (SF-36v2).[22,23] The items from the SF-36v2 can also be used to calculate a health utility score; a score which quantitatively describes the overall health state of an individual.[24] The health utility score varies from 0 (a health state equivalent to death) to 1 (a health state equivalent to perfect health). For example, based on the response pattern of the SF-36v2 questions (eg, a respondent reported their health as "excellent", they experienced no bodily pain, etc; all items from the SF-36v2), they are assigned a health utility score. The higher the health utility score, the better the overall health state of the respondent.

Statistical analysis

The results are presented in two sections. In the first section, demographic and health history differences among clinical insomniacs and good sleepers were examined using chi-square tests and one-way analysis of variance tests (ANOVAs). Effect sizes (Cohen's *d* for continuous variables and ϕ coefficients for categorical variables) were also reported. Differences between these two groups with respect to hrQOL were then examined using multiple linear regressions controlling for age, sex, education, income, smoking, alcohol use, exercise, body mass index, and the CCI. Adjusted means from these regression models were reported.

The second section examined predictors of health utilities among clinical insomniacs using a multiple regression model. Predictors included demographics and health history variables. Unstandardized regression coefficients (b) and the 95% confidence intervals around those coefficients are provided. Adjusted means of different subgroups (eg, patients who exercise) were reported from the results of this model. Post hoc analyses then used the results of this regression model to understand how malleable behavioral factors (smoking, alcohol use, exercise) could potentially influence the health utility values among clinical insomniacs who either had a physical (based on the CCI) or psychiatric comorbidity burden. Among those with a physical comorbidity but not a psychiatric one, those with a psychiatric comorbidity but not a physical one, and those without either a physical or psychiatric comorbidity, the predicted health utility score was generated using the regression equation, assuming 0, 1, 2, or 3 positive health behaviors (ie, no smoking, no alcohol use, regular exercise). These predicted health utility scores were then qualitatively compared to those without insomnia.

Results

The burden of insomnia

A total of 4.9% (n=1,455) of respondents reported a diagnosis of insomnia, with most (70.0% using a prescription medication). These n=1,018 (3.4% of the total adult population) participants who reported having insomnia and using a prescription treatment for their insomnia were defined as clinical insomniacs; n=20,542 were defined as good sleepers. The most common sleep symptoms experienced by clinical insomniacs included waking up several times at night (60.9%), waking up too early (55.7%), waking up and not getting back to sleep (52.9%), and difficulty falling asleep (21.9%). The demographic differences between these groups are shown in Table 1. Several differences were observed between clinical insomniacs and good sleepers. Specifically, clinical insomniacs were more likely to be female ($P<0.01$), have a lower annual household income ($P<0.001$), be unemployed but looking for work ($P<0.001$), and less likely to be employed ($P<0.001$). Clinical insomniacs were also more likely to smoke ($P<0.001$), exercise regularly

Table 1 Demographic and health history differences among clinical insomniacs and good sleepers

	Clinical insomniacs (n=1,018)		Good sleepers (n=20,542)		*P*-value	Cohen's *d*
	Mean	SD	Mean	SD		
Age	47.9	14.7	47.0	15.8	0.080	0.28
CCI	0.41	0.88	0.12	0.41	0.000	0.02
	%	N	%	N	*P*-value	ϕ
Male	46.7%	475	50.9%	10,448	0.009	−0.02
University graduate	44.5%	453	47.0%	9,650	0.081	0.02
Annual income: <¥3 MM	24.2%	246	17.8%	3,666	0.000	0.04
Annual income: ¥3 to <¥5 MM	26.0%	265	26.2%	5,374		
Annual income: ¥5 to <¥8 MM	23.1%	235	25.7%	5,288		
Annual income: ¥8 MM or more	19.7%	201	20.0%	4,113		
Annual income: decline	7.0%	71	10.2%	2,101		
Employed	52.0%	529	59.0%	12,122	0.000	0.06
Not employed and looking for work	7.1%	72	2.7%	552		
Not employed and not looking for work	41.0%	417	38.3%	7,868		
Smoke	34.9%	355	20.2%	4,145	0.000	0.08
Drink alcohol	30.6%	312	30.5%	6,256	0.896	0.00
Regular exercise	44.9%	457	41.6%	8,550	0.039	0.01
BMI: underweight	15.9%	162	10.7%	2,199	0.000	0.06
BMI: normal weight	59.3%	604	68.7%	14,119		
BMI: obese	22.3%	227	16.3%	3,344		
BMI: unknown	2.5%	25	4.3%	880		
Psychiatric comorbidity	51.5%	524	2.2%	459	0.000	−0.51
Physical comorbidity	26.9%	274	9.2%	1,891	0.000	−0.13

Abbreviations: CCI, Charlson comorbidity index; SD, standard deviation; BMI, body mass index; MM, million.

($P<0.05$), be obese ($P<0.001$), and have a higher CCI score ($P<0.001$).

The most common prescription medications used were zolpidem tartrate (26.7%), brotizolam (22.5%), flunitrazepam (21.2%), and etizolam (19.1%) (Table 2). A mean of 1.7 mediations were used by those with insomnia (standard deviation =1.3).

Adjusting for demographic and health history differences, clinical insomniacs reported significantly worse MCS and PCS scores relative to good sleepers (MCS: 34.2 vs 48.0, Cohen's d=1.48, respectively; PCS: 48.0 vs 52.8, Cohen's d=0.79, respectively, both $P<0.001$) (Figure 1). Similarly, clinical insomniacs reported significantly worse health utility scores (0.61 vs 0.76, Cohen's d=1.21, $P<0.001$; Figure 1).

Predicting health status among those treated

Among clinical insomniacs, an analysis of their health utility scores was examined (see Figure 2 for analyzed indices and Supplementary materials for complete regression tables). Employment status was the only demographic variable significantly associated with health utilities; those not employed and looking for work reported significantly lower health utilities (b=−0.035, $P<0.05$) than those employed (the reference group). Smoking (b=−0.016, $P<0.05$) and alcohol use (b=−0.018, $P<0.05$) were associated with lower health utilities while exercise behavior was associated with higher health utility values (b=0.023) ($P<0.001$). Although the CCI was significantly associated with lower health utility

Table 2 Prescription medication use among those with insomnia

	%	N
Zolpidem tartrate	26.7	272
Brotizolam	22.5	229
Flunitrazepam	21.2	216
Etizolam	19.1	194
Triazolam	17.4	177
Alprazolam	7.8	79
Zopiclone	7.3	74
Nitrazepam	6.3	64
Estazolam	4.9	50
Trazodone hydrochloride	4.6	47
Lormetazepam	3.9	40
Rilmazafone hydrochloride	3.3	34
Quazepam	2.8	28
Flurazepam hydrochloride	2.2	22
Mirtazapine	2.0	20
Other	12.9	131
Number of medications used (mean, SD)	1.7	1.3

Abbreviation: SD, standard deviation.

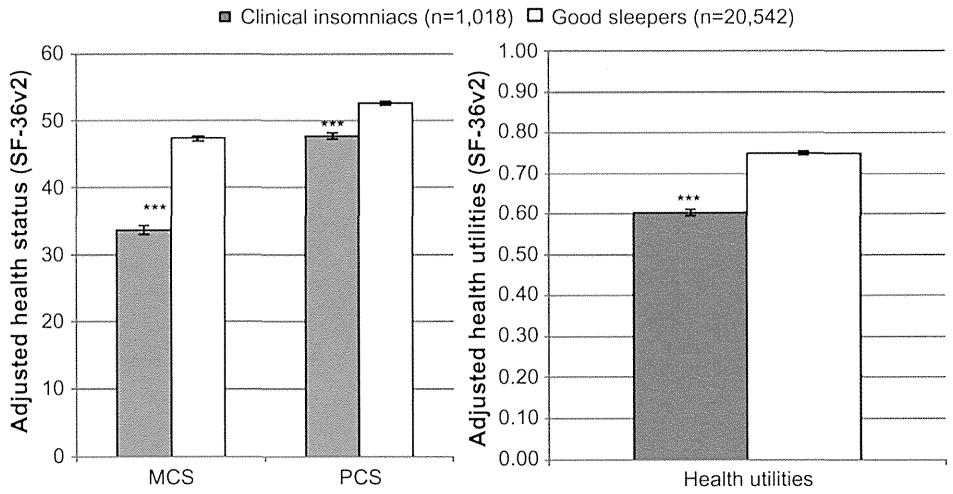

Figure 1 Adjusted means of health status measures (MCS and PCS scores from the SF-36v2) among clinical insomniacs versus good sleepers.
Note: ***$P<0.001$.
Abbreviations: SF, Short Form; MCS, mental component summary; PCS, physical component summary.

values (b=–0.015), the strongest association was psychiatric comorbidities (b=–0.08) (both $P<0.001$).

Using this regression model, subsequent analyses estimated the health utility scores for certain segments of clinical insomniacs. Specifically, health utility scores were estimated for respondents who had a varying number of positive health behaviors (from 0 to 3 of the following: do not smoke, do not drink alcohol, exercise regularly) among different physical and psychiatric comorbidity subgroups (Figure 3). For all three clinical insomniac subgroups of interest, those with a physical comorbidity but not a psychiatric one, those with a psychiatric comorbidity but not a physical one, and those without either a physical or psychiatric comorbidity, large decrements in health utilities were observed for respondents who did not engage in any positive health behaviors (0.61, 0.57, 0.64, respectively) relative to good sleepers (0.78). However, the gap in health utility scores between these subgroups and good sleepers diminishes with an increasing number of positive health behaviors. Indeed, for respondents with a physical comorbidity but not a psychiatric one and for respondents without either a physical or a psychiatric comorbidity who engage in all three positive health behaviors, the

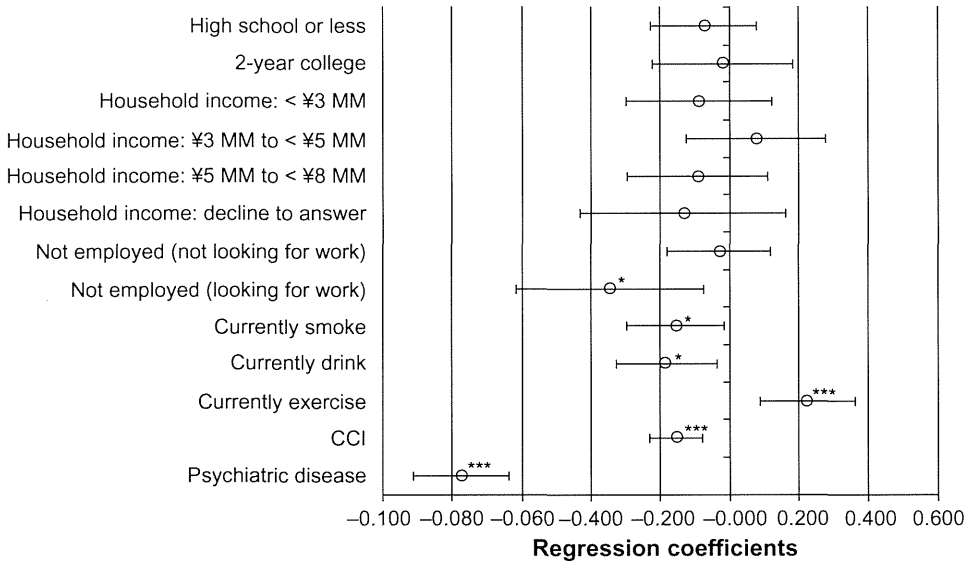

Figure 2 Unstandardized regression coefficients of predictors of health utility scores among clinical insomniacs.
Notes: All variables measured dichotomously with the exception of the CCI. *$P<0.05$; ***$P<0.001$. Bars represent 95% confidence intervals.
Abbreviations: CCI, Charlson comorbidity index; MM, million.

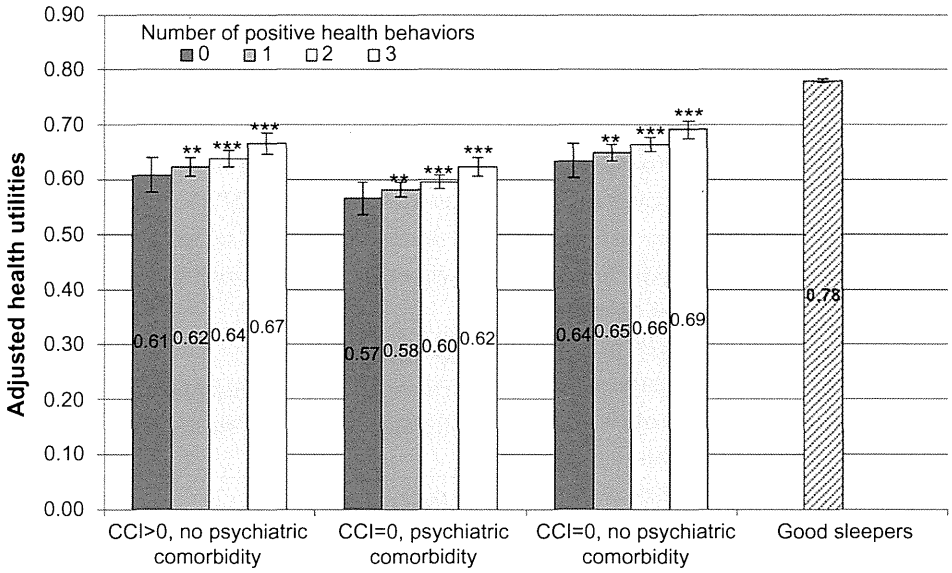

Figure 3 Predicted health utility scores for each clinical insomniac subgroup based on the number of positive health behaviors engaged in (smoking cessation, alcohol abstinence, and regular exercise) compared with good sleepers.

Notes: **$P<0.01$; ***$P<0.001$ relative to "0 positive health behavior" category within each group (ie, those with a CCI >0 and no psychiatric comorbidity; those with CCI =0 and a psychiatric comorbidity; those with CCI =0 and no psychiatric comorbidity). The "good sleepers" bar was provided merely for context and was not part of the statistical model as they, by definition, did not have insomnia. Bars represent 95% confidence intervals.

Abbreviation: CCI, Charlson comorbidity index.

gap in health utilities was reduced to 0.11 and 0.09 points, respectively (0.67 vs 0.78 and 0.69 vs 0.78, respectively). However, due to the strong relationship between psychiatric comorbidities and health utilities, the gap between those with a psychiatric comorbidity still remained large despite the engagement in all three positive behaviors when compared with good sleepers (0.62 vs 0.78).

Discussion

Although this study was not intended to be an epidemiological investigation of insomnia in Japan, our prevalence rate (4.9% of the population was diagnosed; 3.4% of the adult population was diagnosed and treated) was generally consistent with the rates of primary insomnia.[1–3] Naturally, our study does differ from the epidemiological studies which focused on defining insomnia purely through symptoms,[6] as respondents who met criteria for a diagnosis of insomnia based on their symptom profile but have not been diagnosed would be excluded from our study but included in others. The discrepancy in prevalence observed between those who only report symptoms and those who are receiving a diagnosis (the latter further supported by the results here) suggests that a number of patients who meet criteria may not be receiving a diagnosis of insomnia.

It also should be noted that although there are undoubtedly cultural and health care system differences, the prevalence of insomnia and insomnia medication use was generally comparable between Japan and the West suggesting the potential generalizability of the findings.[25–27]

We observed a significant burden for patients with insomnia using a prescription medication (clinical insomniacs) compared with those without insomnia or insomnia symptoms (good sleepers) on hrQOL. This finding was similar to those reported in the United States[18,19] and also extends the research by Sasai et al in Japan.[20] Sasai et al compared differences across those with and without insomnia and those using and not using a medication.[20] Although they had more analysis groups of interest, the authors found significant differences in MCS and PCS between clinical insomniacs and good sleepers, as reported here.[6] However, our analyses controlled for a wider array of confounding variables (eg, CCI, health behaviors, etc) to provide further evidence of this effect. Despite the treatment they are receiving, clinical insomniacs still experience significant and clinically relevant decrements in hrQOL variables. These decrements are observed even after controlling for health history and comorbidity variables, reinforcing the effect insomnia has on patient functioning. This may, in part, be due to a lack of treatment benefit with respect to hrQOL. However, it is likely to be more than just a lack of effectiveness that is causing this gap. Certain sleep medications can be associated with dependency and residual effects, which could reduce levels of hrQOL.[28] Further, although we controlled for both physical