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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

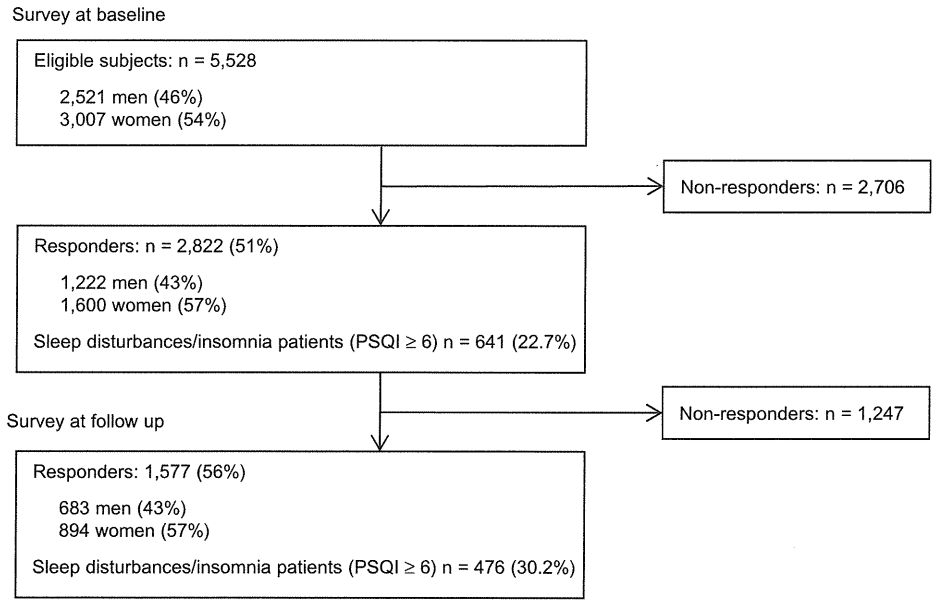


Fig. 1. Survey flowchart.

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.

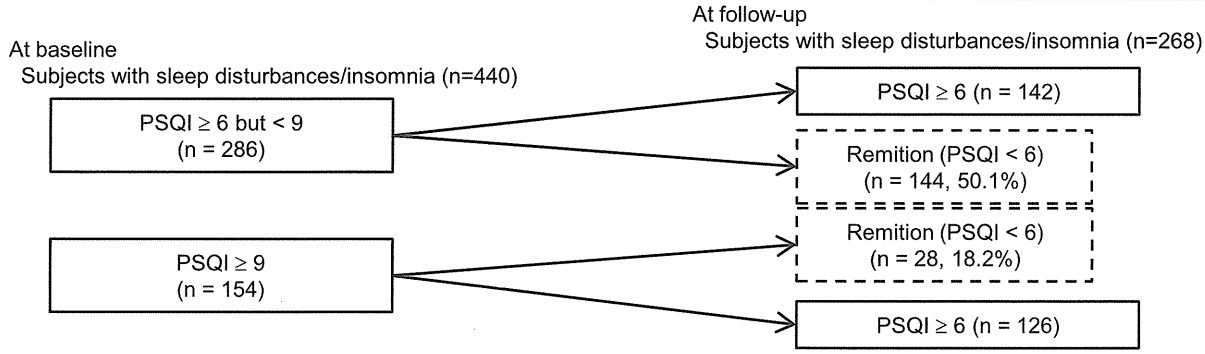
When we examined longitudinal QoL data among persistent poor sleepers, neither the MCS nor PCS scores differed significantly over the 2-year course. Thus, a modest aggravation of sleep disturbances/insomnia symptoms may not necessarily lead to a deterioration of daytime functioning over time.

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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Scientific Research

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 χ^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 χ^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).

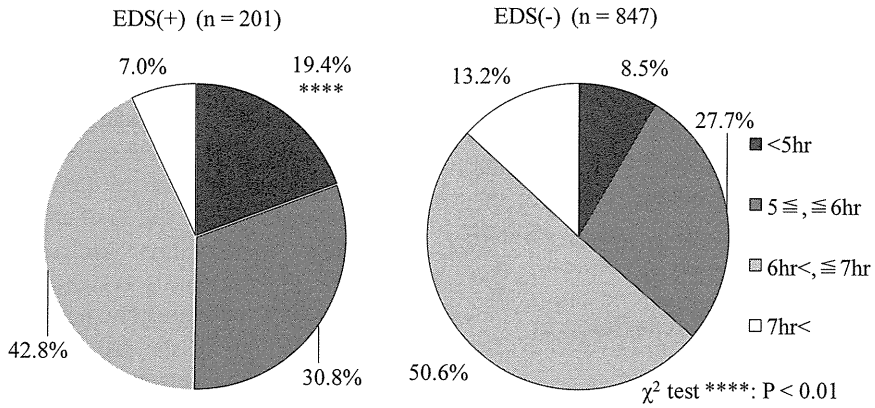
Variable	OR (95%CI)	P value
Age	0.99 (0.97 - 1.00)	0.052
Sex	1.85 (0.94 - 3.64)	0.074
%usage ≧ 4 h/d	1.00 (1.00 - 1.01)	0.327
global PSQI-J scores	1.29 (1.22 - 1.36)	<0.001

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.

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ORIGINAL RESEARCH

Group cognitive behavioral therapy for patients with generalized social anxiety disorder in Japan: outcomes at 1-year follow up and outcome predictors

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Background: Social anxiety disorder (SAD) is one of the most common psychiatric disorders worldwide. Cognitive behavioral therapy (CBT) is an effective treatment option for patients with SAD. In the present study, we examined the efficacy of group CBT for patients with generalized SAD in Japan at 1-year follow-up and investigated predictors with regard to outcomes.

Methods: This study was conducted as a single-arm, naturalistic, follow-up study in a routine Japanese clinical setting. A total of 113 outpatients with generalized SAD participated in group CBT from July 2003 to August 2010 and were assessed at follow-ups for up to 1 year. Primary outcome was the total score on the Social Phobia Scale/Social Interaction Anxiety Scale (SPS/SIAS) at 1 year. Possible baseline predictors were investigated using mixed-model analyses.

Results: Among the 113 patients, 70 completed the assessment at the 1-year follow-up. The SPS/SIAS scores showed significant improvement throughout the follow-ups for up to 1 year. The effect sizes of SPS/SIAS at the 1-year follow-up were 0.68 (95% confidence interval 0.41–0.95)/0.76 (0.49–1.03) in the intention-to-treat group and 0.77 (0.42–1.10)/0.84 (0.49–1.18) in completers. Older age at baseline, late onset, and lower severity of SAD were significantly associated with good outcomes as a result of mixed-model analyses.

Conclusions: CBT for patients with generalized SAD in Japan is effective for up to 1 year after treatment. The effect sizes were as large as those in previous studies conducted in Western countries. Older age at baseline, late onset, and lower severity of SAD were predictors for a good outcome from group CBT.

Keywords: social phobia, cognitive behavior therapy, psychotherapy

Introduction

Social anxiety disorder (SAD), often referred to as social phobia, is characterized by fear and avoidance of social situations. Epidemiological surveys have shown that SAD is the fourth most common psychiatric disorder,[1] with a lifetime prevalence of 12%.[2] SAD begins during adolescence and often persists.[3] Patients with SAD often suffer from comorbid depression[4,5] and other anxiety disorders.[6] According to such characteristics of the disorder, SAD causes significant social dysfunction, and patients with SAD frequently develop functional impairment at work and in their private lives, which decreases their quality of life.[7,8] Therefore, providing appropriate treatment for SAD is important.

Previous studies have provided evidence that pharmacotherapy,[9] including benzodiazepines, selective serotonin-reuptake inhibitors, and monoamine oxidase inhibitors,

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are effective during SAD treatment as well as during cognitive behavioral therapy (CBT).[10] A number of randomized controlled trials[11,12] and strong evidence for a positive effect of CBT on SAD have been published. The effect size of CBT has been estimated at 0.71 (95% confidence interval [CI] 0.56–0.85) by a recent meta-analysis,[13] and it showed lower relapse rates than treatments based on pharmacotherapy.[14]

Some researchers have demonstrated the effectiveness of CBT in a group format. Because patients with SAD are often anxious and avoid small-group work, they can be exposed to fearful situations by attending sessions.[10] Furthermore, group CBT has greater cost-effectiveness compared with individual CBT.[15]

From 2003 onward, we conducted group CBT for outpatients with SAD at the Department of Psychiatry, Nagoya City University Hospital, based on previous studies. Our preliminary posttreatment data (from July 2003 to January 2007, n = 57) show that group CBT is acceptable.[16] We have also published the long-term (1-year) effects on quality of life[17] (n = 57) and symptomatology[18] (n = 62) in patients with SAD. These studies examined the baseline predictors of the outcomes, but none were found. These studies[16–18] also had limitations because of small sample size, and many dropout cases made it difficult to identify predictors. Furthermore, we included both the generalized and nongeneralized subtypes of SAD in these studies. Although both subtypes can be improved by CBT, the generalized subtype has more severe social anxiety symptoms and social function disability than those of the nongeneralized subtype, and patients are more impaired prior to and after treatment.[19] Our previous studies may have contaminated efficacy by including both subtypes.

To overcome these limitations, in the present study we accumulated twice the number of participants (n = 113) as in our previous studies,[16–18] and we focused on the generalized subtype to present more conclusive data. Moreover, we adopted a mixed-model analysis, which is considered the most effective way to identify treatment outcome predictors. Many studies have attempted to identify predictors of treatment outcomes, but only a few specific predictors have been found.[20] Baseline predictors may enable us to provide CBT more effectively and to prevent dropout from treatment.

Furthermore, although CBT was originally developed in Western countries, some previous studies have discussed the cultural boundaries of SAD symptoms or SAD treatment.[21,22] A condition called "taijin kyofusho" syndrome occurs in Japan and some other East Asian countries, as stated in the appendix of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV). From this perspective, exploring the efficacy of CBT for SAD has a significant meaning in Japan.

Thus, we conducted this study with the aim of identifying the long-term efficacy and predictors of group CBT for patients with generalized SAD in Japan.

Methods

Subjects

From July 2003 to August 2010, 113 outpatients with SAD were enrolled in the group-based CBT program at the Department of Psychiatry, Nagoya City University Hospital, Japan. All patients fulfilled the criteria for generalized SAD as the primary disorder according to the structured clinical interview for the DSM-IV. Furthermore, all patients met the following criteria: (1) no history of psychosis or bipolar disorder, or current substance-abuse disorder, (2) no previous CBT treatments, with agreement not to be involved in any other structured psychosocial therapies during treatment, and (3) absence of cluster B personality disorder. We included patients with current axis I disorders if symptoms were controlled sufficiently to allow joining a group session. For example, we included major depressive disorder or other current anxiety disorders or patients with axis II personality disorders except criterion (3).

All patients gave written informed consent after a full explanation of the study. This study was approved by the ethics committee of the Nagoya City University Graduate School of Medical Sciences.

Treatments

This study was conducted as a single-arm, naturalistic, follow-up study in a routine Japanese clinical setting. We followed the CBT manual for SAD written by Andrews et al,[23] and we modified and improved the program according to Clark and Wells' model.[24] Treatment was conducted in groups of three patients led by one principal therapist and one cotherapist, and were scheduled for 120 minutes once per week.

The average number of sessions was 14 (range 12–20), depending on the needs of each group. The program included (1) psychoeducation about SAD (session 1), (2) introduction about the individual cognitive behavioral model of SAD (session 2), (3) experiments to drop safety behavior and self-focused attention (from session 8 to last session), (4) attention training to shift focus away from themselves to the task or the external social situation (sessions 4 and 5), (5) video feedback of role-playing in anxious situations to modify their self-image (sessions 6 and 7), (6) in vivo exposure using behavioral experiments to test the patient's catastrophic

predictions (from session 8 to last session), and (7) cognitive restructuring (session 3, from session 8 to last session). We assigned homework to the patients after every session. Among 113 patients, 98 patients (86.7%) completed CBT, and almost all of the patients (n = 109) finished all the exercise kinds, even when they were absent from a few sessions.

Eight therapists (five psychiatrists and three doctoral-level clinical psychologists), with more than 3 years of clinical practice with anxiety disorders, conducted the treatment program. Adherence to the treatment manual was monitored by group discussion once per month. We allowed patients to use antidepressants and benzodiazepines during CBT, because our study was based in a clinical setting and there is some evidence for combined pharmacologic/CBT therapy.[11,25] Patients did not participate in any other structured psychotherapy while attending group CBT.

Assessment

The principal therapist conducted the mood- and anxiety-disorder sections of the structured clinical interview for the DSM-IV at baseline, for the SAD diagnosis, and any mood and anxiety comorbidities.

Patients' demographic data were gathered at baseline, including such sociodemographic factors as sex, age, educational status, marital status, and employment status. Information about age of onset and duration of SAD, SAD subtype, psychiatric comorbidities, and medication use was also obtained.

The patients were assessed with self-report questionnaires at baseline, post-treatment, and by mail at the 1-year follow-up. Our primary outcome was the total Social Phobia Scale/Social Interaction Anxiety Scale (SPS/SIAS)[26] score at the 1-year follow-up.

SPS/SIAS

The SPS and SIAS are 20-item self-report questionnaires with ratings on a 4-point scale from 0 (not at all characteristic or true of me) to 4 (extremely characteristic or true of me), and total scores of 0–80. A high score indicates severe symptoms. The SPS measures the fear of being observed, whereas the SIAS provides a measure of fear of social interaction. Sufficient internal consistency, reliability, and discrimination, as well as predictive and concurrent validity have been demonstrated for both original and Japanese versions.[27] Cronbach's alphas of our sample for SPS/SIAS were 0.88/0.60–0.88.

Fear Questionnaire social phobia subscale

The Fear Questionnaire social phobia subscale (FQ-sp)[28] is a 5-item self-reported instrument for measuring the fear-motivated avoidance of being observed, performing, being criticized, and talking to authorities. Items are rated on a 9-point Likert-type scale, from 0 (would not avoid it) to 8 (always avoid it). A high score indicates severe symptoms. Good test–retest reliability and factor validity have been demonstrated.[29]

Statistical analyses

We compared treatment completers with patients who dropped out using unpaired *t*-tests for continuous variables or chi-square tests for categorical variables. We also calculated Cohen's *d* for the continuous variables. Treatment completers were defined as participants who had attended at least 80% of all treatment sessions and completed posttreatment and 1-year follow-up questionnaires.

The pretreatment and 1-year follow-up scores on SPS/SIAS were compared using paired *t*-tests to quantify outcomes from the CBT program. Furthermore, to examine the outcomes of the CBT program across various aspects of the disorder, pre- and posttreatment scores were compared for SPS, SIAS, and FQ-sp using paired *t*-tests, and pretreatment and 1-year follow-up were compared for FQ-sp using paired *t*-tests. To show the magnitude of the treatment effect, we calculated the effect size (M pretest – M posttest)/pooled standard deviation [SD]. All statistical analyses for these treatment outcomes were conducted twice: once based on the intention-to-treat (ITT) principle and once among the completers only. The ITT analyses were conducted using the last-observation-carried forward (LOCF) model, for which we used the mid-treatment data (after the eighth session) or the 3-month follow-up data, whichever were the last observational data available. We used the LOCF model to present more conservative treatment-effectiveness estimates.

We conducted mixed-model analyses to detect the baseline predictors of treatment outcome with the 1-year follow-up SPS/SIAS score as a dependent variable and the baseline demographic and clinical variables (sex, age, marital status, educational status, employment status, onset, duration of SAD, current mood disorder, current anxiety disorder, antidepressant use at baseline, benzodiazepine use at baseline, number of treatment sessions, severity) as variables. We converted continuous variables into categorical variables for this analysis. Age and onset of SAD age were categorized by Medline search criteria (age was divided into three categories: 13–18 years, 19–45 years, and ≥46 years; onset of SAD was divided into three categories: ≤12 years of age, 13–18 years of age, and 19–45 years of age). The number of treatment sessions was divided into

Table 1 Demographic and diagnostic characteristics of the patients and a comparison of treatment completers and dropouts

	Total	Dropout	Completers	*P* value
	113	43	70	
Gender (%)				
Female	56 (49.6)	19 (44.2)	37 (0.53)	0.37
Male	57 (50.4)	24 (55.9)	33 (47.1)	
Age Mean (SD)	31.8 (10.4)	30.0 (9.9)	32.9 (10.5)	0.14
Education (%)				
University	34 (30.1)	8 (18.6)	26 (37.1)	0.10
College	16 (14.2)	5 (11.7)	11 (15.7)	
High school	58 (51.3)	27 (62.8)	31 (44.2)	
Junior high school	5 (4.4)	3 (7.0)	2 (2.9)	
Marital status (%)				
Married	39 (34.5)	15 (34.9)	24 (34.3)	0.99
Separated/divorced	3 (2.7)	1 (2.3)	2 (2.9)	
Single, never married	71 (62.8)	27 (62.8)	44 (62.9)	
Employment (%)				
Full-time employment	23 (20.4)	6 (14.0)	17 (24.3)	0.07
Full-time student	20 (17.7)	12 (28.0)	8 (11.4)	
Part-time/homemaker/retired	46 (40.7)	14 (32.6)	32 (45.7)	
Unemployed	24 (21.2)	11 (25.6)	13 (18.6)	
Onset of SAD, mean (SD)	17.3 (5.9)	15.1 (4.7)	18.7 (6.2)	0.001
Duration of SAD, mean (SD)	14.3 (11.5)	15.0 (11.4)	13.8 (11.6)	0.62
Number of sessions taken, mean (SD)	14.0 (3.6)	11.7 (4.4)	15.5 (1.8)	<0.005
Benzodiazepine use at baseline (%)	37 (32.7)	11 (25.6)	26 (37.1)	0.2
Antidepressant use at baseline (%)	58 (51.3)	21 (49.0)	37 (52.9)	0.68
Current mood disorder (%)	27 (23.9)	12 (10.6)	15 (13.3)	0.5
Current anxiety disorder (%)	11 (9.7)	4 (3.5)	7 (6.2)	1.0
FQ-sp score at baseline	24.7 (6.2)	24.3 (6.4)	24.9 (6.1)	0.58
SPS total score at baseline	37.8 (14.4)	43.2 (15.2)	34.4 (12.8)	0.002
SIAS total score at baseline	56.0 (12.5)	57.8 (13.9)	54.8 (11.6)	0.24

Abbreviations: FQ-sp, Fear Questionnaire social phobia subscale; ITT, intention-to-treat; SAD, social anxiety disorder; SIAS, Social Interaction Anxiety Scale; SPS, social phobia scale.

two categories according to our definition of minimal session number (n = 12). We divided the variable of duration of SAD into two categories of ≤1 year or >1 year, because we wanted to explore the effectiveness of early treatment intervention. Baseline severity of SAD was defined by the baseline SPS total score, based on Heimberg et al,[30] with more than 34 being defined as severe.

All the statistical tests were two-tailed, and an alpha value of less than 0.05 was considered statistically significant. All the data were examined using SPSS 19.0 (IBM, Armonk, NY, USA) for Windows.

Results

Demographic and diagnostic characteristics of patients and comparison of treatment completers and dropouts

One hundred and thirteen outpatients with SAD (57 males and 56 females; age range 14–63 years; mean ± SD 31.8 ± 10.4 years) were enrolled in our study. Table 1 summarizes the

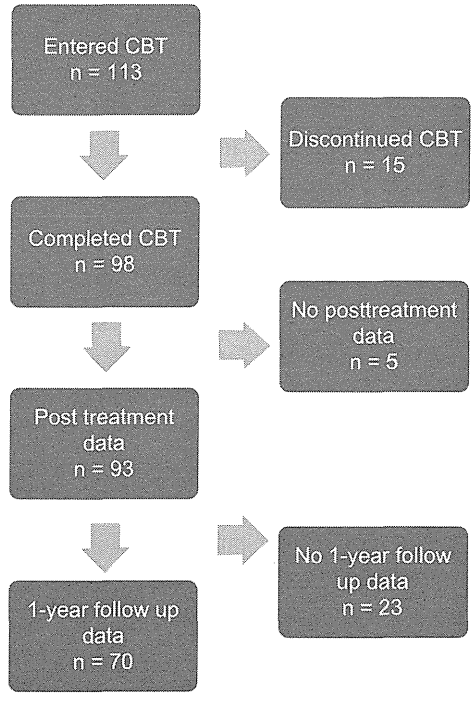

Figure 1 Number of patients at different time points.
Abbreviation: CBT, cognitive behavioral therapy.

Table 2 ITT and completers mean symptom scores and SDs at the pre- and post-treatment

Mean (SD)	ITT (N = 113)			Completers (N = 70)		
	Pre	Post	*P* value	Pre	Post	*P* value
FQ-sp score	24.6 (6.3)	19.6 (8.6)	<0.05	24.9 (6.1)	19.1 (8.2)	<0.05
SPS total score	37.8 (14.4)	28.1 (15.7)	<0.05	34.4 (12.8)	24.6 (13.0)	<0.05
SIAS total score	56.0 (12.5)	45.4 (15.2)	<0.05	54.8 (11.6)	44.6 (13.5)	<0.05

Abbreviations: FQ-sp, Fear Questionnaire social phobia subscale; ITT, intention-to-treat; SIAS, Social Interaction Anxiety Scale; SPS, social phobia scale.

demographic and clinical characteristics of the patients and compares treatment completers with dropouts. All participants met the principal diagnostic criteria for the DSM-IV SAD generalized subtype.

As a result of chi-square tests for categorical variables, onset of SAD and SPS total score at baseline showed $P < 0.05$, but no other major differences were observed between completers and dropouts. The number of sessions taken by patients on average was 14 (range 12–20).

Figure 1 shows the number of patients at different time points. Of the 113 patients who were enrolled, 98 completed treatment and 70 finished the 1-year follow-up. Although pre- and posttreatment SPS were not normally distributed, we conducted analyses as we planned, because the other measures were normally distributed.

Changes in symptoms and function through treatment

Table 2 shows the mean symptom scores and SDs of all measures for all participants (ITT population using the LOCF model) and pre- and posttreatment completers and pre- and 1-year follow-ups. An examination of the change in symptom measures (SPS, SIAS, and FQ-sp) between pre- and posttreatment and between pre- and 1-year follow-ups revealed significant improvements not only for the completers but also for the ITT samples (all $P < 0.05$).

Next, the effect sizes for each symptom measure were calculated, and the results are presented in Tables 4 and 5. The effect sizes for the total SPS/SIAS scores at the 1-year follow-up, which was our primary outcome, were 0.68 (95% CI 0.41–0.95)/0.76 (95% CI, 0.49–1.03) in the ITT sample and 0.77 (0.42–1.10)/0.84 (0.49–1.18) in completers. Based on the ITT sample analyses, effect sizes for assessment at posttreatment were SPS 0.64 (0.37–0.90), SIAS 0.76 (0.49–1.03), and FQ-sp 0.66 (0.39–0.93), and at 1-year follow-up FQ-sp was 0.76 (0.48–1.02).

Effect sizes for treatment completers at posttreatment were SPS 0.81 (95% CI, 0.46–1.15), SIAS 0.76 (0.49–1.10), and FQ-sp 0.81 (0.47–1.15), and the effect size of the FQ-sp at 1-year follow up was 0.96 (0.61–1.31), indicating a greater change than that in the ITT sample.

All effect sizes were larger at 1-year follow-up than those at posttreatment.

Predictors of treatment outcomes at 1-year follow-up

Table 6 summarizes the mixed-model analyses outcome. A significant difference was found for SIAS in the older age-group at baseline ($P = 0.019$), a lower severity on SPS ($P = 0.000$), and late onset of SAD for both SPS ($P = 0.001$) and SIAS ($P = 0.000$) as predictors of good treatment outcome.

Discussion

Main findings

The results indicate the long-term efficacy of a CBT program for Japanese patients with SAD generalized subtype. Although we focused on patients with the generalized subtype, who have more severe symptoms than those with the nongeneralized subtype, the effect sizes were as large as those in a meta-analysis conducted in Western countries[13] and our previous study at posttreatment.

Table 3 ITT and completers mean symptom scores and SDs at the pre-treatment and 1-year follow ups

Mean (SD)	ITT (N = 113)			Completers (N = 70)		
	Pre	1-year	P value	Pre	1-year	P value
FQ-sp score	24.6 (6.3)	19.2 (7.9)	<0.05	24.9 (6.1)	18.3 (7.7)	<0.05
SPS total score	37.5 (14.4)	27.3 (16.1)	<0.05	34.4 (12.8)	24.1 (14.1)	<0.05
SIAS total score	56.0 (12.5)	45.4 (15.2)	<0.05	54.8 (11.6)	43.7 (14.9)	<0.05

Abbreviations: FQ-sp, Fear Questionnaire social phobia subscale; ITT, intention-to-treat; SIAS, Social Interaction Anxiety Scale; SPS, social phobia scale.

Table 4 Effect sizes for ITT and completers at the pre- and post-treatment compared with our previous study

	ITT (N = 113)	Previous study ITT (N = 57)	Completers (N = 70)	Previous study completers (N = 50)
FQ-sp score	0.66	1.01	0.81	1.19
(95% CI)	(0.39–0.93)		(0.46–1.15)	
SPS total score	0.64	0.75	0.76	0.83
(95% CI)	(0.37–0.90)		(0.41–1.10)	
SIAS total score	0.76	0.79	0.81	0.89
(95% CI)	(0.49–1.03)		(0.47–1.15)	

Abbreviations: FQ-sp, Fear Questionnaire social phobia subscale; ITT, intention-to-treat; SIAS, Social Interaction Anxiety Scale; SPS, social phobia scale.

According to the effect-size calculation, our treatment program had significant effects at posttreatment that were maintained until the 1-year follow-up. This outcome is the same as that of a previous study, which demonstrated the maintenance efficacy of CBT[14] and indicates the possibility that patients are able to use treatment elements by themselves after group treatment.

Few CBT therapists are available for SAD treatment in Japan, and national health insurance does not include CBT for anxiety disorders. Thus, accumulating evidence for a positive effect of CBT in Japan is a matter of urgency, and we hope our study contributes to this purpose. Group CBT is more cost-effective than individual CBT in this regard, and we would like to diffuse this effective treatment for SAD in Japan.

We investigated baseline predictors for treatment outcomes. A number of studies have examined the role of particular variables in predicting the response to treatment; however, results have been inconsistent and inconclusive.[20] The severity of comorbid depression,[31,32] symptomatic severity,[31] avoidant personality disorder,[33] and expectancy[32] have been suggested as possible follow-up predictors for group CBT.

Although some demographic variables (female, married, higher education) were possible follow-up predictors in a study[34] that conducted individual CBT, and the aforementioned demographic variables were not statistically significant in our group CBT study, we believe that suitable characteristics of patients are different between group CBT and individual therapy.

We found that older age, late onset of SAD, and less severe symptoms on SPS were possible baseline treatment predictors for a good outcome. These results agreed with our clinical impression. We may have to pay more attention to patients who are contrary to those features by reflecting on those results.

Future studies should focus not only on pretreatment variables but also on the treatment process, such as homework compliance and the client–therapist relationship, as suggested by Scholing and Emmelkamp.[31] These factors may help improve the clinical practice of CBT for SAD.

Limitations

The present study had several limitations. First, this study was conducted in a routine Japanese clinical setting as a single-arm, naturalistic, follow-up study. Thus, a random control trial is needed to estimate the conservative efficacy of treatment.

Second, antidepressant and benzodiazepine medications were allowed during treatment, but information about the amount of drug consumption during the course was not collected. We are unable to consider dose effects of medications on CBT; however, use of medication at baseline was not a significant predictor of treatment outcomes in the present study.

Third, some may argue that there were no patients with avoidant personality disorder in our study. We used the structured clinical interview of the DSM-IV mood/anxiety module, but we did not use other modules considering patient load. We only excluded patients who were clinically diagnosed with personality B disorders in accordance with group therapy. The diagnosis of avoidance personality disorder is difficult, as is distinguishing between severe generalized SAD and avoidant personality disorder, thus we

Table 5 Effect sizes for ITT and completers at the pre-treatment and 1-year follow ups

	ITT (N = 113)	Completers (N = 70)
FQ-sp score	0.76	0.96
(95% CI)	(0.48–1.02)	(0.61–1.31)
SPS total score	0.68	0.77
(95% CI)	(0.41–0.95)	(0.42–1.10)
SIAS total score	0.76	0.84
(95% CI)	(0.49–1.03)	(0.49–1.18)

Abbreviations: FQ-sp, Fear Questionnaire social phobia subscale; ITT, intention-to-treat; SIAS, Social Interaction Anxiety Scale; SPS, social phobia scale.