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Daytime light exposure in daily life and depressive symptoms in bipolar disorder: A cross-sectional analysis in the APPLE cohort

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ABSTRACT

Objectives: Controlled artificial daylight exposure, such as light therapy, is effective in bipolar depression, but the association between uncontrolled daytime light and depressive symptoms in bipolar disorder (BD) is unclear. This study investigated the association between daytime light exposure under real-life situations and depressive symptom in patients with BD.

Methods: This cross-sectional study enrolled 181 outpatients with BD. The average daytime light intensity and the total duration of light intensity of ≥1000 lux were recorded over 7 consecutive days using an actigraph that measured ambient light. Depressive symptoms were assessed using Montgomery–Åsberg Depression Rating Scale, and scores of ≥8 points were treated as depressed state.

Results: Ninety-seven (53.6%) subjects were depressed state. At higher average daytime light intensity tertiles, the proportion of depressed state was significantly lower (*P* for trend, 0.003). In multivariable analysis adjusted for age, employment status, age at onset of BD, Young Mania Rating Scale score, bedtime, and physical activity, the highest tertile group in average daytime light intensity suggested a significantly lower odds ratio (OR) for depressed state than the lowest tertile group (OR, 0.33; 95% confidence interval [CI], 0.14–0.75; *P* = 0.009). Similarly, the longest tertile group in light intensity ≥1000 lux duration was significantly associated with lower OR for depressed state than lowest tertile group (OR, 0.42; 95% CI, 0.18–0.93; *P* = 0.033).

Conclusions: The findings suggest that greater daytime light exposure in daily life is associated with decreased depressive symptoms in BD.

1. Introduction

Bipolar disorder (BD) is a recurrent chronic disorder characterized by episodes of depression and mania/hypomania that affects > 1% of the world's population (Grande et al., 2016). In its clinical course, patients with BD spend more time with depressive symptoms than with mania/hypomania (Judd et al., 2002, 2003). Depressive symptoms are associated with a socioeconomic burden, a burden on caregivers, functional impairment, and reduced quality of life of the patient (Miller et al., 2014), and suicide or suicide attempts mostly occur during the depressive episodes of BD (Hauser et al., 2013). Thus, reducing depressive symptoms is important in the management of patients with BD.

Light exposure is closely associated with depressive symptoms. Light therapy (LT), which typically involves the use of artificial light of 2500–10,000 lux for a period of 30 min–2 h in the morning (Pail et al., 2011), has been recommended as the first-line treatment for seasonal affective disorder by American Psychiatric Association (2000). A meta-analysis reported that LT used as treatment for 567 patients with bipolar depression significantly reduced the severity of depressive symptoms compared with treatment without LT, indicating a medium effect (Hedge's g = 0.69) (Tseng et al., 2016). In a recent randomized controlled trial, patients with bipolar depression who received adjunctive LT at midday exhibited significantly lower depression scores than those receiving the placebo treatment with dim light (Sit et al., 2018). These findings indicate that controlled artificial daylight exposure is effective for depressive symptom in patients with BD.

Daylight exposure in uncontrolled settings has also been reported to be associated with reduced depressive symptoms in BD patients and the

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general population. A retrospective study reported shorter lengths of hospitalization for patients with bipolar depression staying in east-facing rooms, which were exposed to direct sunlight in the morning, compared to those staying in west-facing rooms (Benedetti et al., 2001). A study of healthy subjects reported that exposure to less light during the daytime was significantly associated with low mood (Terao and Hoaki, 2011). Another study also showed that office workers who received high levels of light exposure in the morning were less likely to suffer depressive symptom than those receiving low levels of light (Figueiro et al., 2017). The results of a recent meta-analysis and a randomized controlled trial have suggested that exposure to artificial light in the morning or at midday is effective for bipolar depression (Sit et al., 2018; Tseng et al., 2016); therefore, it is likely that daylight exposure in daily life can reduce depressive symptoms associated with BD. However, to the best of our knowledge, no study has investigated whether the level of daytime light exposure under real-life situations is associated with depressive symptoms in outpatients with BD.

We hypothesized that greater daytime light exposure in real-life situations is associated with decreased depressive symptoms in patients with BD. In this study, we investigated the association between daytime light exposure, measured using a light meter, and depressive symptoms in patients with BD.

2. Material and methods

2.1. Clinical sample

A total of 187 outpatients with BD were enrolled into the Association Between the Pathology of Bipolar Disorder and Light Exposure in Daily Life (APPLE) cohort study between August 2017 and November 2018. The patients were recruited from Okehazama Hospital, Fujita Mental Care Satellite Zengo, Fujita Mental Care Satellite Tokushige, and Fujita Health University. The inclusion criteria were age 18–75 years and a diagnosis of BD I or II according to the Diagnostic and Statistical Manual of Mental Disorders (fifth edition). Night shift workers and those judged by a clinician to be at serious risk of suicide were excluded. Five patients discontinued the study because of discomfort with wearing the actigraph, and depressive symptoms could not be evaluated in one patient. As a result, data for 181 patients were analyzed. The study was approved by the Ethics Committee of Okehazama Hospital. Written informed consent was obtained from all the participating patients, and the study was registered at UMIN-CTR (identifier: UMIN000028239).

2.2. Procedure

The participants were assessed for demographic and clinical characteristics at the clinic and were then asked to wear an actigraph that could measure ambient light (Actiwatch Spectrum Plus; Respironics Inc., Pittsburgh, PA, USA) on the wrist of their non-dominant arm for 24 h/day for seven consecutive days, except during bathing and aquatic activities. The participants were instructed not to cover the actigraph with their clothing and tuck their sleeves up using the armband, if necessary. They were also asked to record their bedtime and rising time in sleep diary. Bedtime was defined as the time that the participant went to bed with the intention to sleep, excluding time spent in bed reading books or watching television. Rising time was defined as the time the participant finally got out of bed.

2.3. Daytime light exposure assessment

The analysis included light exposure measured using the actigraph at 1-min intervals throughout the period between the participant's rising time and bedtime, as recorded in his or her sleep diary. Any periods during which the actigraph was not worn were automatically excluded by the detection algorithm in Actiware version 6.0.9 software (Respironics Inc.); if this extended to more than half of the daytime period, the data for that day were treated as missing. Any data recorded as < 1 lux during the daytime period were considered to be artifacts caused by clothing covering the actigraph and were excluded from the analysis (Scheuermaier et al., 2010). Two daytime light exposure parameters were used: the average light intensity for the period between rising time and bedtime (the "average light intensity") and the total number of minutes during each daytime period for which the light intensity was recorded as ≥ 1000 lux (the "≥ 1000 lux duration").

2.4. Depressive symptom assessment

Depressive symptoms were objectively assessed using the Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). This is a ten-item diagnostic questionnaire that measures the severity of depressive symptoms in patients with mood disorders. The overall score is in the range 0–60, with higher scores indicating more severe depression. The International Society for Bipolar Disorders (ISBD) Task Force recommended that a MADRS score of ≤ 7 could be considered indicative of symptomatic remission of bipolar depression (Tohen et al., 2009). We therefore treated the MADRS score of ≥ 8 points as depressed state.

2.5. Other assessments

Physical activity and sleep were evaluated objectively using actigraphy. Sleep periods were defined by a default threshold of fewer than 40 activity counts per min, which has been shown to be as accurate as polysomnography for measuring sleep in patients with BD (Kaplan et al., 2012). Two actigraphy sleep parameters were used in this study: total sleep time (TST), defined as the total time spent asleep between bedtime and rising time, excluding wake after sleep onset; and sleep efficiency, defined as TST as a percentage of the total time between bedtime and rising time. Daytime physical activity was evaluated as the average activity count per minute during the period from rising time to bedtime. Manic symptoms were assessed using the Young Mania Rating Scale (YMRS) (Young et al., 1978). Information on medications was retrieved from the participants' clinical records, including the use of lithium, anticonvulsants (lamotrigine, valproate, and carbamazepine), antipsychotics, antidepressants, and hypnotics (benzodiazepine hypnotics, ramelteon, and suvorexant). The final doses of antipsychotics, antidepressants, and benzodiazepine hypnotics were determined based on chlorpromazine-, imipramine-, and diazepam-equivalent doses, respectively (Hayasaka et al., 2015; Inada and Inagaki, 2015; Leucht et al., 2016). For each participant, the length of the first measurement day in Aichi (latitude, 35°N) from sunrise to sunset was obtained from the web page of the National Astronomical Observatory of Japan.

2.6. Statistical analyses

Normally distributed variables are summarized as mean and standard deviation (SD), those with an asymmetrical distribution as median and interquartile range (IQR), and categorical variables as number and percentage. Means and medians were compared between the depressed and not depressed groups using the unpaired t-tests and the Mann–Whitney *U* test, respectively. Fisher's exact test and the chi-square test were used to compare categorical data. Univariate comparisons were made between the depressed and not depressed groups for the variables of demographic characteristics (age, gender, marriage status, education level, employment status), clinical characteristics (type of BD, age at onset of BD, duration of illness, MADRS and YMRS scores, family history, and day length), medications (lithium, anticonvulsants, antipsychotics, antidepressants, and hypnotics), daytime light parameters (average light intensity and ≥ 1000 lux duration), daytime physical activity, and sleep parameters (bedtime, rising time, TST, and sleep efficiency).

Logistic regression models were used to evaluate trend of the proportion of depressed state associated with tertiles of average light intensity (Low, Intermediate, High) or ≥1000 lux duration (Short, Intermediate, Long). Odds ratios (ORs) for depressed state, with Low or Short as reference, were evaluated using univariable and multivariable logistic regression models. The YMRS score was not normally distributed, even after log transformation. It was, therefore, treated as a categorical variable in the logistic regression analyses as being either above or below a cutoff value of 5 points (the cutoff value for mania recommended by the ISBD Task Force) (Tohen et al., 2009). In the multivariable models, the ORs were adjusted for the variables in the univariable comparisons that were significantly associated ($P < 0.05$) with depressed state (Tables 1 and 2). The statistical analyses were performed using SPSS version 25.0 for Windows (IBM Corp., Armonk, NY). A two-sided P value < 0.05 was considered statistically significant.

3. Results

The mean (SD) age of the 181 participants included in the analysis was 45.5 (13.2) years and 101 (56%) of the participants were women. The median (IQR) of the MADRS scores was 8.0 (3.0–14.0), and 97 (53.6%) participants were depressed state. The medians (IQRs) of average light intensity and ≥1000 lux duration were 226.5 (155.8–307.2) lux and 29.6 (17.1–47.9) min, respectively.

Table 1 compares the demographic characteristics, clinical characteristics, and medications used between the depressed and not depressed groups. The depressed group were significantly lower age (43 vs. 48.5 years), employment status (35.4% vs. 50.0%), and age at onset of BD (31.0 vs. 35.2 years) than in the not depressed group. YMRS score was significantly higher in the depressed group than in the not depressed group (3.0 vs. 2.0 points). The proportion of medications used in the depressed and not depressed groups were lithium (40.2% vs. 40.5%), anticonvulsant (59.8% vs. 53.6%), antipsychotic (58.8% vs. 50.0%), antidepressant (36.1% vs. 35.7%). The use of the medications, including the combination therapy, did not differ significantly between the two groups.

Table 2 presents the light, physical activity, and sleep parameters

Table 2
Comparisons of daytime light parameters, physical activity, and sleep parameters between the depressed and not depressed groups.

Variables	Mood status		
	Depressed (n = 97)	Not depressed (n = 84)	P
Daytime light parameter, median (IQR)			
Average light intensity, lux	200.6 (138.8–278.7)	265.2 (179.3–351.5)	< 0.01
≥1000 lux duration, min	28.0 (15.0–39.7)	37.6 (20.2–55.4)	< 0.01
Daytime physical activity, counts/min, mean (SD)	167.1 (60.3)	192.5 (80.4)	0.01
Sleep parameters, mean (SD)			
Bedtime, clock time	23:31 (1:54)	22:50 (1:28)	< 0.01
Rising time, clock time	7:21 (2:08)	6:58 (1:38)	0.18
Total sleep time, min	378.7 (97.1)	401.5 (92.8)	0.11
Sleep efficiency, %	81.9 (8.2)	82.6 (9.2)	0.60

Data are expressed as mean (standard deviation) or median (interquartile range).

Table 1
Demographic and clinical characteristics of the participants in the depressed and not depressed groups.

Variables	Mood status		
	Depressed (n = 97)	Not depressed (n = 84)	P
Demographic characteristics			
Age, years, mean (SD)	43.0 (11.7)	48.5 (14.3)	< 0.01
Gender, female, n (%)	60 (61.9)	41 (48.8)	0.08
Married, n (%)	50 (51.5)	47 (56.0)	0.55
Education (≥13 years), n (%)	52 (54.2)	51 (60.7)	0.37
Employed, n (%)	34 (35.4)	42 (50.0)	0.048
Clinical characteristics			
Type of BD, BD I, n (%)	34 (38.1)	29 (35.7)	0.73
Age at onset of BD, years, mean (SD)	31.0 (11.0)	35.2 (13.1)	0.02
Duration of illness, years, mean (SD)	12.0 (8.7)	13.3 (9.2)	0.35
MADRS score, points, median (IQR)	13.0 (11.0–22.0)	2.5 (1.0–5.0)	< 0.01
YMRS score, points, median (IQR)	3.0 (1.0–5.0)	2.0 (0–4.0)	0.02
Family history of psychiatric disorders, n (%)	16 (16.7)	15 (17.9)	0.83
Day length, min, median (IQR)	773.0 (681.0–838.5)	746.0 (674.5–819.0)	0.26
Medications			
Lithium, n (%)	39 (40.2)	34 (40.5)	0.97
Anticonvulsant, n (%)	58 (59.8)	45 (53.6)	0.39
Lamotrigine, n (%)	36 (37.1)	25 (29.8)	0.29
Valproate, n (%)	23 (23.7)	22 (26.2)	0.70
Carbamazepine, n (%)	3 (3.0)	0 (0)	0.10
Antipsychotic, n (%)	57 (58.8)	42 (50.0)	0.23
Antipsychotics, mg/day, median (IQR)†	25.0 (0–227.5)	39.3 (0–183.7)	0.81
Antidepressant, n (%)	35 (36.1)	30 (35.7)	0.95
Antidepressants, mg/day, median (IQR)‡	0 (0–71.6)	0 (0–75.0)	0.86
Benzodiazepine hypnotic, n (%)	53 (54.6)	37 (44.0)	0.15
Benzodiazepine hypnotics, mg/day, median (IQR)§	2.4 (0–6.5)	0 (0–5.0)	0.11
Ramelteon, n (%)	9 (9.3)	4 (4.8)	0.24
Suvorexant, n (%)	19 (19.6)	19 (22.6)	0.61
Lithium + Anticonvulsant, n (%)	18 (18.6)	10 (11.9)	0.21
Lithium + Antipsychotic, n (%)	24 (24.7)	17 (20.2)	0.47
Anticonvulsant + Antipsychotic, n (%)	32 (33.0)	21 (25.0)	0.23
Lithium + Anticonvulsant + Antipsychotic, n (%)	13 (13.4)	6 (7.1)	0.17

Data are expressed as mean (standard deviation), median (interquartile range [IQR]), or number (percentage).
† Chlorpromazine-equivalent dose; ‡ imipramine-equivalent dose; § diazepam-equivalent dose. BD, bipolar disorder; MADRS, Montgomery–Åsberg Depression Rating Scale; YMRS, Young Mania Rating Scale.

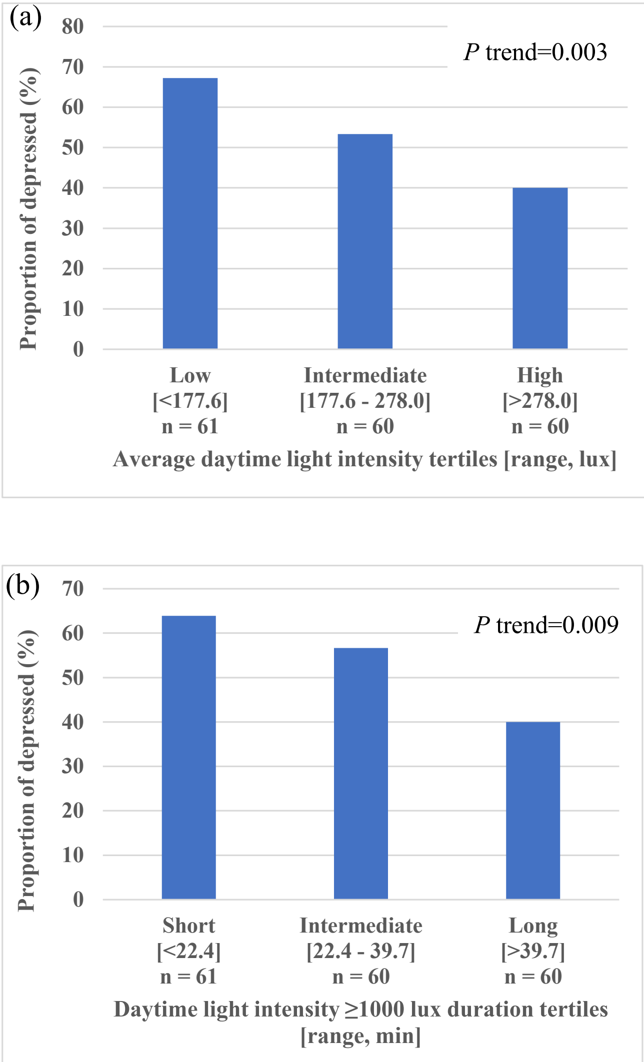

Fig. 1. Associations between tertiles for average daytime light intensity (a) and total duration of light intensity ≥1000 lux (b) and the proportion of depressed state at each tertile. *P* values are for the trends analyzed using logistic regression analysis.

for the depressed and not depressed groups. Average light intensity and ≥1000 lux duration were significantly lower for the depressed group than for the not depressed group (average light intensity: 200.6 vs. 265.2 lux; ≥1000 lux duration: 28.0 vs. 37.6 min). In addition, daytime physical activity was significantly lower in the depressed group than in the not depressed group (167.1 vs. 192.5 counts/min), and bedtime was significantly later (23:31 vs. 22:50 clock time).

Tertiles were calculated for average light intensity and ≥1000 lux duration. As the tertile increased, the proportion of depressed state was significantly lower (average light intensity: Low, 67.2%; Intermediate, 53.3%; High, 40.0%; *P* for trend, 0.003; ≥1000 lux duration: Short, 63.9%; Intermediate, 56.6%; Long, 40.0%; *P* for trend, 0.009; Fig. 1). In the univariable logistic regression analysis, unadjusted ORs for depressed state significantly decreased as the tertile increased for both of the daytime light parameters (average light intensity: Low, 1.00; Intermediate, 0.55; High, 0.32; *P* for trend, 0.003; ≥1000 lux duration: Short, 1.0; Intermediate, 0.73; Long, 0.37; *P* for trend, 0.009; Tables 3 and 4). In the multivariable logistic regression analysis, after adjusting for age (per year), employment status (yes or no), age at onset of BD (per year), YMRS score (≥5 or < 5 points), bedtime (late or early: category based on the median value), and daytime physical activity (per

Table 3
Logistic regression analysis for the association between tertiles for average light intensity and odds ratios (ORs) for depressed state.

	Average light intensity tertiles			
	Low	Intermediate	High	*P* trend
	< 177.6 lux	177.6–278.0 lux	> 278.0 lux	
Unadjusted OR (95% CI)	1.00 (ref)	0.55 (0.26–1.16)	0.32 (0.15–0.68)	0.003
Adjusted OR (95% CI)	1.00 (ref)	0.62 (0.28–1.38)	0.33 (0.14–0.75)	0.009

Data are expressed as odds ratios (95% confidence interval). Adjusted for the variables significantly associated ($P < 0.05$) with depressed in Tables 1 and 2 (age, age at onset of bipolar disorder, employment status, Young Mania Rating Scale score, bedtime, and daytime physical activity).

count/min), higher average light intensity tertiles showed a significantly lower OR for depressed state than did lower average light intensity tertiles (High vs. Low: OR, 0.33; 95% confidence interval [CI], 0.14–0.75; *P* = 0.009; Table 3). Consistently, longer ≥1000 lux duration tertiles was significantly associated with lower ORs for depressed state than shorter ≥1000 lux duration tertiles (Long vs. Short: OR, 0.42; 95% CI, 0.18–0.93; *P* = 0.033; Table 4).

4. Discussion

This was the first study to explore associations between daytime light exposure in daily life and depressive symptoms in BD. The results showed that the average intensity of daytime light exposure was significantly associated with depressed state in patients with BD. Multivariable analyses suggested that this association was independent of several potential confounding factors. The main finding was supported by a significant association between the total duration of light intensity ≥1000 lux and depressive symptoms.

These findings appear to be consistent with the results of previous studies on the effectiveness of LT in bipolar depression. A meta-analysis showed that the disease severity in 567 patients with BD significantly decreased after treatment with LT, yielding an effect size of 0.69 (Hedges' g) (Tseng et al., 2016), and a recent randomized controlled trial reported that adjunctive bright LT at midday for bipolar depression resulted in a significantly higher remission rate compared with the use of placebo dim light (68.2% vs. 22.2%) (Sit et al., 2018). Similarly, our results indicated that OR for depressed state was 67% lower in patient with BD in the higher average daytime light intensity tertile than the OR for those in the lower tertile group. Previous studies have shown that controlled light exposure was effective for bipolar depression, but the present study provided evidence that uncontrolled daytime light exposure in daily life was also significantly associated with depressive

Table 4
Logistic regression analysis for the association between tertiles for total duration of light intensity ≥1000 lux and odds ratios (ORs) for depressed state.

	Light intensity ≥1000 lux duration tertiles			*P* trend
	Short	Intermediate	Long	
	< 22.4 min	22.4–39.7 min	> 39.7 min	
Unadjusted OR (95% CI)	1.00 (ref)	0.73 (0.35–1.53)	0.37 (0.18–0.78)	0.009
Adjusted OR (95% CI)	1.00 (ref)	0.92 (0.41–2.05)	0.42 (0.18–0.93)	0.033

Data are expressed as odds ratios (95% confidence interval). Adjusted for the variables significantly associated ($P < 0.05$) with depressed in Tables 1 and 2 (age, age at onset of bipolar disorder, employment status, Young Mania Rating Scale score, bedtime, and daytime physical activity).

symptoms in BD.

Although various studies have suggested that LT provides effective for patients with BD undergoing a current depressive episode (Chojnacka et al., 2016; Sit et al., 2018; Yorguner Kupeli et al., 2018; Zhou et al., 2018), evidence for its long-term efficacy is scarce, and studies have reported a risk of hypomania with LT (Sit et al., 2007; Tuunainen et al., 2004). Additionally, few hospitals and clinics have the capability to provide LT in daily clinical practice. Conversely, outdoor light has an intensity of at least 3000 lux on cloudy days and tens of thousands of lux on a sunny day (Dharani et al., 2012). This light intensity is similar to or higher than that of LT. A retrospective study reported that BD inpatients who were directly exposed to sunlight in the morning had a shorter hospital stay (by a mean of 3.67 days) than those who were not directly exposed (Benedetti et al., 2001). It may therefore be important to explain to patients with BD the importance of spending time outdoors during the day.

Till date, the mechanism underlying the association between daytime light exposure and depressive symptoms is unknown. Reportedly, light exposure is associated with circadian phase shift (Khalsa et al., 2003), melatonin secretion (Obayashi et al., 2012), and glucose metabolism in the left cerebellar vermis (Hirakawa et al., 2018). These are associated with depressive symptoms (Kitamura et al., 2010; Mayberg et al., 1988; Obayashi et al., 2015). Thus, light exposure is involved in multiple mechanisms; however, it is unclear which of these mechanisms contribute to the improvement of depressive symptoms. Further studies are warranted to determine whether any of these processes mediate between daytime light exposure and depressive symptoms in BD.

This study had several strengths and limitations. The strength was the consistency of results between the two daytime light exposure parameters, average daytime light intensity and total duration of light intensity ≥1000 lux. Another of its strengths was the objective measurement of depressive symptoms and light exposure. The first limitation was that this was a cross-sectional study, so the findings do not necessarily imply that daytime light exposure reduces depressive symptoms in patients with BD. Depressive episodes are states of decreased energy, malaise, or fatigue. These symptoms may cause a decrease in physical activity, and, as a result, the opportunity of outdoor light exposure may be reduced. However, our results showed that daytime light exposure was significantly associated with depressive symptoms independent of the daytime physical activity. Further research using a longitudinal and controlled design is needed to determine whether the association between daytime light exposure and bipolar depression is causal. Second, the study participants were not randomly selected; they were recruited at our hospitals and clinics. The results may therefore have been affected by selection bias. Third, we did not investigate the weather during the measurement period. For example, rain or cloudiness may have influenced the daytime light exposure and the participant's behavior. Finally, daytime light exposure was recorded only for seven days, and the average daytime light intensity for those seven days may not be the correct representative value for that period. However, we speculate that a period of seven days provides an approximate representation of an individual's behavior pattern because it includes both weekdays and weekend.

In conclusion, the findings of this study showed a significant association between greater daytime light exposure and lower depressive symptoms in patients with BD. Further investigation is necessary to confirm the association between daytime light exposure in daily life and bipolar depression.

Conflicts of interest

The authors report no conflicts of interest related to this research. Dr. Kitajima has received speaker's honoraria from Eisai, Mitsubishi Tanabe, Otsuka, Takeda, Eli Lilly, MSD, Meiji, Yoshitomi, Fukuda, Dainippon Sumitomo, Shionogi, and Novo Nordisk, and has received a research grant from Eisai, MSD and Takeda. Dr. Obayashi and Dr. Saeki has received a research grant from YKK AP Inc.; Ushio Inc.; Tokyo Electric Power Company; EnviroLife Research Institute Co., Ltd.; Sekisui Chemical Co., Ltd; LIXIL Corp.; and KYOCERA Corp. Dr. Fujita has received speaker's honoraria from Dainippon Sumitomo, Eli Lilly, GlaxoSmithKline, Janssen, Yoshitomi, Otsuka, Meiji, Shionogi, Novartis, and Kracie. Dr Iwata has received speaker's honoraria from Astellas, Dainippon Sumitomo, Eli Lilly, GlaxoSmithKline, Janssen, Yoshitomi, Otsuka, Meiji, Shionogi, Novartis, and Pfizer and has had research grants from GlaxoSmithKline, Meiji, Otsuka, Mitsubishi Tanabe, Dainippon Sumitomo, Daiichisankyo, and Eisai.

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