Solar insolation in springtime influences age of onset of bipolar I disorder

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Objective: To confirm prior findings that the larger the maximum monthly increase in solar insolation in springtime, the younger the age of onset of bipolar disorder.

Method: Data were collected from 5536 patients at 50 sites in 32 countries on six continents. Onset occurred at 456 locations in 57 countries. Variables included solar insolation, birth-cohort, family history, polarity of first episode and country physician density.

Results: There was a significant, inverse association between the maximum monthly increase in solar insolation at the onset location, and the age of onset. This effect was reduced in those without a family history of mood disorders and with a first episode of mania rather than depression. The maximum monthly increase occurred in springtime. The youngest birth-cohort had the youngest age of onset. All prior relationships were confirmed using both the entire sample, and only the youngest birth-cohort (all estimated coefficients $P < 0.001$).

Conclusion: A large increase in springtime solar insolation may impact the onset of bipolar disorder, especially with a family history of mood disorders. Recent societal changes that affect light exposure (LED lighting, mobile devices backlit with LEDs) may influence adaptability to a springtime circadian challenge.

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Significant outcomes

- There was a strong, inverse association between the maximum monthly increase in solar insolation in springtime and the age of onset of bipolar I disorder using a global sample. The effect was reduced in those without a family history of mood disorders.
- There was a large birth-cohort effect, with the youngest group having the youngest onset. Major societal changes that may affect vulnerability to a circadian challenge need investigation: exposure to LED lighting, mobile devices backlit with LEDs, and the 24-h society.

Limitations

- The data collection process was not standardized. Data on family history or age of onset may be unreliable.
- There was no individual data on behaviours or exposures that affect circadian rhythms.
- The sample was not demographically representative of the country populations.

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Introduction

There is considerable evidence of circadian rhythm dysfunction in patients with bipolar disorder including disturbances in the sleep/wake cycle, activity patterns, melatonin secretion, as well as suggestive associations with clock gene polymorphisms and epigenetic alterations (1–6). Clinical symptoms that are frequently reported include sleep timing disturbances (7), irregular daily schedules (8), and an evening preference (9). These symptoms of circadian disruption may occur during episodes, while euthymic (7, 10–13), and in those at high risk for bipolar disorder (7, 12, 14, 15). Even small changes to circadian rhythms such as the shift to daylight savings time may have adverse mental health consequences (16). In the future, circadian symptoms and clock gene polymorphisms may help define endophenotypes of bipolar disorder, including early onset (17–19).

Some of the current treatments for bipolar disorder act directly or indirectly on circadian mechanisms, which may contribute to therapeutic effects (2). Lithium modulates the expression of central and peripheral clock genes (20–23), and the amplitude and timing of effects may differ between responders and non-responders (24). Lithium also has phase-delaying properties and may resynchronize overly fast circadian rhythms (2, 21). Other treatments for bipolar disorder that may modify circadian systems include valproate (2, 25) light and dark therapy and sleep deprivation (1, 26), and blue light blocking glasses (27).

The importance of the circadian system to human health is becoming clearer from recent research, as summarized briefly. Over the course of evolution, life on Earth has adapted to the Sun (28). Humans have endogenous circadian timing cycles for nearly every physiological, metabolic, and behavioural system allowing for anticipation of light and dark, and adaptation to seasonal changes and environmental challenge (29–31). The cycle length of endogenous circadian rhythms is not exactly 24 h and must be regularly synchronized to the natural 24-h light–dark cycle that arises from one rotation of the Earth on its axis (32). Sunlight is the primary and most potent signal that entrains human circadian systems to the natural environment. Specialized non-visual receptors, photosensitive retinal ganglion cells (pRGC), express the melanopsin photopigment that is sensitive to short-wavelength blue light (33). The pRGC detect environmental fluctuations in light and project primarily to non-visual centers of the brain including the suprachiasmatic nucleus (SCN) in the hypothalamus (34). The SCN is the master pacemaker over a system that includes circadian clock genes expressed in the SCN, and throughout the rest of the brain, peripheral tissues and cells (35, 36). The signals from the pRGC entrain the SCN (37), which integrates the external signals with signals from internal activities, and in turn entrains the peripheral circadian clocks (35, 36). Timekeeping for optimal diurnal physiological processes and mental health requires both synchronization of the circadian systems with the natural environment, and internal system-wide circadian coordination.

Aims of the study

As the onset of bipolar disorder is highly variable, it is important to understand the factors that may influence it, including environmental (38, 39). We previously found a large, significant, inverse relation between the maximum monthly increase in solar insolation (incoming solar radiation striking the Earth's surface) and the age of onset of bipolar I disorder (40, 41). This effect was reduced in those without a family history of mood disorders and was smaller for those with a first episode of mania rather than depression. The aim of this analysis was to confirm that the relations found previously were not sample specific, by repeating the analyses using significantly more data from geographically dispersed countries.

Methods

The data were collected by researchers at 50 collection sites in 32 countries. In the Northern Hemisphere, the collection sites were Aalborg, Denmark; Aarhus, Denmark; Ankara, Turkey; Athens, Greece; Bangalore, India; Barcelona,

Spain; Beer Sheva, Israel; Cagliari, Italy (2 sites); Calgary, Canada; Dresden, Germany; Halifax, Canada; Helsinki, Finland; Hong Kong; Hyderabad, India; Kampala, Uganda; Kansas City, KS, USA; Khanti-Mansiysk, Russia; Kuala Lumpur, Malaysia; Los Angeles, CA, USA; Medellín, Colombia; Mexico City, Mexico; Oslo, Norway; Ottawa, Canada; Palo Alto, CA, USA; Paris, France; Poznan, Poland; Rochester, MN, USA; San Diego, CA, USA; Siena, Italy; Singapore; Stockholm/Gothenburg, Sweden; Tartu, Estonia; Thessaloniki, Greece; Tokyo, Japan; Trondheim, Norway; Tunis, Tunisia; Vitoria, Spain; Wiener Neustadt, Austria; Worcester, MA, USA, and Würzburg, Germany. In the Southern Hemisphere, the collection sites were: Adelaide, Australia; Buenos Aires, Argentina; Cape Town, South Africa; Melbourne/Geelong, Australia; Porto Alegre, Brazil; Salvador, Brazil; Santiago, Chile (2 sites); and São Paulo, Brazil. This analysis combined newly collected data with data collected and analyzed previously.

Approval for this study was obtained from local institutional review boards according to local requirements. All patients had a diagnosis of bipolar disorder according to DSM-IV criteria from a psychiatrist, with age of onset defined as the first occurrence of an episode of mania, hypomania, or depression. Other patient data in this analysis were sex, family history of a mood disorder in any first degree relative, and polarity of the first episode. Data were obtained retrospectively by direct questioning, reviewing records, or both.

Solar insolation

Solar insolation is defined as the amount of electromagnetic energy from the Sun received on Earth for a given surface area at a given time, expressed in kilowatt h/square meter/day ($kWh/m^2/day$) (42). Several factors determine the intensity of solar insolation including the angle at which the Sun's rays strike the Earth's surface, time of day, latitude, atmospheric conditions, surface reflection, and the Earth's tilt. The tilt of Earth's axis relative to the plane of its orbit around the Sun results in the seasonal changes in solar insolation and day length (43). The pattern of monthly changes in solar insolation varies by latitude, with very little monthly change near the equator and larger monthly changes as one nears the poles. However, locations at the same latitude may have different patterns due to local conditions such as altitude, cloud cover, and proximity to bodies of water.

All solar insolation data were obtained from the National Aeronautics and Space Administration (NASA) Surface Meteorological and Solar Energy (SSE) database version 6.0, which is based on global data collected by satellite for 22 years between 1983 and 2005 (42). The average monthly solar insolation data are available with a spatial resolution of $1° \times 1°$ latitude/longitude. The actual onset locations were grouped into reference onset locations, which represent all locations in the $1° \times 1°$ grid of latitude and longitude. The number of reference onset locations from a collection site varied greatly, influenced by country size, migration patterns, and cultural factors. The reference onset locations were used in all analyses. All solar insolation data were shifted by 6 months for onset locations in the Southern Hemisphere to compare with data from the Northern Hemisphere. Solar insolation is an appropriate variable for a sample with multiple birth-cohorts as the incoming global average, annual mean solar insolation has remained essentially unchanged over the last 2000 years (44).

The monthly change in solar insolation was calculated as the difference between the current month minus the previous month. The maximum monthly increase in solar insolation was defined as the largest monthly increase over the year. The interaction between the maximum monthly increase in solar insolation × family history and the maximum monthly increase in solar insolation × polarity of first episode were also analyzed.

Birth-cohort

The birth-cohort was included in all analyses as an older age of onset of bipolar disorder in older cohorts was reported in many studies (40, 41, 45–47). Three birth-cohort groups were created, for those born before 1940, born between 1940 and 1959, and born 1960 or later, consistent with prior research (40, 41, 45–47). In this sample, 34.6% of the patients with bipolar I disorder were born before 1960.

Country specific variables

As the onset of bipolar disorder spans several decades, an older mean age of onset would be expected in a country with an older median age (48, 49), and country median age was included in the prior analyses. The country median age also provides information about country socioeconomic characteristics (50). However, in the current sample, there was a 31-year difference in median age between the oldest country (Japan 46.9 years) and the youngest (Uganda 15.7 years) and more socioeconomic variation among countries.

Additional socioeconomic measures were obtained to explain country specific differences in age of onset: physician density of any specialty per 1000 population, GDP per capita, total health expenditures as a per cent of GDP, and the Gini index of income inequality (50).

Bipolar I disorder

Only data from patients with a diagnosis of bipolar I disorder were included to be consistent with our prior studies, and because there was a large imbalance in the per cent of patients with a diagnosis of bipolar I disorder at the collection sites, varying from 99% to 23%. Also, there was a potential for bias related to age of onset for those who received a diagnosis before the criteria were expanded to include bipolar II disorder.

Statistics

Estimates of the effects of solar insolation on the age of onset were calculated using generalized estimating equations (GEE) to account for the correlated data and unbalanced number of data points within each onset location (cluster). The GEE model uses a population-based or marginal approach to estimate the effect across the entire population rather than within a cluster (51). An exchangeable correlation matrix was selected for the GEE models, which is appropriate for a large number of clusters including many with a single observation (52). Models were estimated for all patients, and after excluding the patients born before 1960 as in our prior studies. In all GEE models, the dependent variable was the age of onset. Sidak's adjustment for multiple comparisons was used to make pair-wise comparisons between the birth-cohorts. A significance level of 0.01 was used for all evaluations. The corrected quasi-likelihood independence model criterion was used to assist with model evaluation (53). SPSS version 24 (IBM, Armonk, NY, USA) was used for all analyses.

Results

Patients and onset locations

Data were collected for 7392 patients with bipolar disorder. Of these, 5536 had a diagnosis of bipolar I disorder and were included in the analysis. Of the 5536 patients, 3221 (58.2%) were female, and 2314 (41.8%) were male. Family history was available for 4698 of the 5536 patients (84.9%), and of the 4698 patients, 2567 (54.6%) had a positive family history. The polarity of the first episode was available for 5055 of the 5536 patients (91.3%), and of the 5055 patients, the polarity was mania in 2543 (50.3%) and depression in 2512 (49.7%). The unadjusted mean age of onset was 25.4 ± 10.6 years.

The onset of bipolar disorder for the 5536 patients occurred in 456 unique onset locations in 57 countries. The average number of patients in each onset location was 12.1, with 240 of the 5536 patients (4.3%) in an onset location of one. Of the 5536 patients, 4283 (77.4%) had onset in the Northern Hemisphere and 1253 (22.6%) in the Southern Hemisphere (Table 1). The number of patients, onset locations, and onset countries in this study was considerably larger than in our prior studies (Table 2).

Solar insolation

The largest maximum monthly increase in solar insolation occurred in the northern latitudes such as the Nordic countries, Russia, Estonia, and Canada, and in warm dry areas in Chile, USA, Mexico, Greece, and South Africa. The smallest changes occurred near the equator in Uganda, Colombia, Malaysia, and Brazil (Table 3). The maximum monthly increase in solar insolation occurred in springtime in both hemispheres.

Table 1. Latitude of patient onset locations

Degrees latitude (north and south)*	Number of patients	Number of onset locations
0–9	473	30
10–19	413	54
20–29	315	34
30–39	1957	120
40–49	1654	157
50–59	464	46
60–69	259	14
70–79	1	1
Total	5536	456

*1253 in the Southern Hemisphere.

Table 2. Number of patients by study

Study date	Number of patients with bipolar I disorder	Number of onset locations	Number of onset countries
2012 (40)	2414	180	24
2014 (41)	4037	318	43
2017	5536	456	57
Per cent increase between 2012 and 2017 studies (%)	129	153	138
Per cent increase between 2014 and 2017 studies (%)	37	43	33

Excluding the locations near the equator that have little change to solar insolation throughout the year, the maximum increase occurred between February and March at 41.1% of onset locations, between March and April at 35.4% of onset locations, and between April and May at 13.4% of onset locations.

Model estimates

The best model to assess the relation between solar insolation and the age of onset included the interaction of the maximum monthly increase in solar insolation × family history, the birth-cohort and the physician density, as shown in Table 4. There was a significant inverse relation between the

Table 3. Some examples of the maximum monthly increase in solar insolation at onset locations

Onset location	Maximum monthly increase in solar insolation (kWh/m^2/day)	Latitude
Kampala, Uganda	0.3	0.3 N
Medellín, Colombia	0.3	6.3 N
Hong Kong	0.6	22.5 N
Kuala Lumpur, Malaysia	0.6	3.2 N
Salvador, Brazil	0.6	12.9 S
Bangalore, India	0.7	12.9 N
São Paulo, Brazil	0.7	23.5 S
Tokyo, Japan	0.7	35.7 N
Singapore	0.7	1.3 N
Hyderabad, India	0.8	17.4 N
Mexico City, Mexico	0.9	19.4 N
Boston, MA, USA	1.0	42.2 N
Rochester, MN, USA	1.0	44.0 N
Porto Alegre, Brazil	1.0	30.0 S
Nova Scotia, Canada	1.1	45.1 N
Adelaide, Australia	1.1	34.9 S
Thessaloniki, Greece	1.1	40.6 N
Tunis, Tunisia	1.1	36.8 N
Melbourne, Australia	1.1	37.5 S
Barcelona, Spain	1.2	41.4 N
Paris, France	1.2	48.9 N
Ankara, Turkey	1.2	39.9 N
San Diego, CA, USA	1.2	32.4 N
Buenos Aries, Argentina	1.2	34.6 S
Cagliari, Sardinia, Italy	1.3	39.2 N
Dresden, Germany	1.3	51.1 N
Bordeaux, France	1.3	44.8 N
Calgary, Canada	1.4	51.1 N
Beer Sheva, Israel	1.4	31.2 N
Valparaiso, Chile	1.4	33.0 S
Tartu, Estonia	1.4	58.4 N
Athens, Greece	1.5	38.0 N
Los Angeles, CA, USA	1.5	34.0 N
Santiago, Chile	1.5	33.3 S
Helsinki, Finland	1.5	60.2 N
Cape Town, South Africa	1.5	33.9 S
Talca, Chile	1.6	35.4 S
Oslo, Norway	1.6	59.9 N
Khanti-Mansiysk, Russia	1.6	61.0 N
Stockholm, Sweden	1.6	59.3 N
Trondheim, Norway	1.7	63.4 N

maximum monthly increase in solar insolation and the age of onset, labeled Model 1. For every 0.1 kWh/m^2/day increase in the maximum monthly increase in solar insolation, there was approximately a 0.57-year (6.8 months) decrease in the age of onset. Alternatively, comparing the largest (1.7) to the smallest (0.3) maximum monthly increase in solar insolation, Model 1 suggests an 8-year decrease in the age of onset (1.4 range in maximum monthly increase in solar insolation * −5.702 estimated coefficient). This effect was reduced by about 30% if there was no family history. The inverse relation was also found when including the interaction of the maximum monthly increase in solar insolation × polarity of first episode, the birth-cohort and the physician density, labeled Model 2, with the effect about 20% smaller for a first episode of mania (5.3 months). The results were similar when models 1 and 2 were estimated excluding the patients born before 1960 and the birth-cohort (Models 3 and 4 in Table 5).

Of the 5536 patients, 287 (5.1%) were born before 1940, 1631 (29.5%) were born between 1940 and 1959, and 3618 (65.4%) were born in 1960 or later. The birth-cohort was significantly associated with age of onset ($P < 0.001$). In Model 1, compared to the youngest birth-cohort born in 1960 or later, those born before 1940 had an onset 15.7 years older, and those born between 1940 and 1959 had an onset 7.7 years older.

The model estimates were improved when physician density was used to explain socioeconomic differences rather than the country median age (40, 41). Because the model has changed, these results cannot be directly compared with our prior studies. The other economic variables were not significant or the models were not as good. The collection site was considered to be an adequate proxy for the onset location at some sites: Barcelona, Cape Town, Helsinki, Melbourne/Geelong, Salvador, Stockholm/Gothenburg, and Würzburg. The best models were estimated excluding all data from these collection sites and results remained significant ($P < 0.001$). Compared with other solar insolation variables, models including the maximum monthly increase in solar insolation remained the best.

Discussion

Despite increasing the number of patients, onset locations, and countries, the findings from our prior studies were confirmed. The maximum monthly increase in solar insolation was inversely associated with the age of onset of bipolar disorder. The effect was reduced in those without a

Table 4. Estimated coefficients of parameters explaining age of onset of bipolar I disorder

Parameters	Coefficient estimate	Standard error	99% Confidence interval		Coefficient significance	
			Lower	Upper	Wald chi-square	P
Model 1* N = 4698						
Maximum monthly increase in solar insolation	−5.702	0.932	−8.102	−3.301	37.423	<0.001
No family history × maximum monthly increase in solar insolation	1.733	0.247	1.097	2.369	49.288	<0.001
Model 2† N = 5055						
Maximum monthly increase in solar insolation	−5.491	1.008	−8.088	−2.895	29.685	<0.001
First episode manic × maximum monthly increase in solar insolation	1.037	0.269	0.345	1.729	14.901	<0.001

*Dependent variable: Age of Onset. Model: intercept, physicians per 1000 onset country population, maximum monthly increase in solar insolation, no family history × maximum monthly increase in solar insolation and birth-cohort group.
†Dependent variable: Age of Onset. Model: intercept, physicians per 1000 onset country population, maximum monthly increase in solar insolation, first episode manic × maximum monthly increase in solar insolation and birth-cohort group.

Table 5. Estimated coefficients of parameters explaining age of onset for patients with bipolar I disorder born in 1960 or later

Parameters	Coefficient estimate	Standard error	99% Confidence interval		Coefficient significance	
			Lower	Upper	Wald chi-square	P
Model 3* N = 3101						
Maximum monthly increase in solar insolation	−4.676	0.838	−6.835	−2.517	31.118	<0.001
No family history × maximum monthly increase in solar insolation	1.240	0.255	0.584	1.897	23.694	<0.001
Model 4† N = 3308						
Maximum monthly increase in solar insolation	−4.626	0.831	−6.766	−2.487	31.023	<0.001
First episode manic × maximum monthly increase in solar insolation	1.524	0.279	0.805	2.242	29.854	<0.001

*Dependent variable: Age of Onset. Model: intercept, physicians per 1000 onset country population, maximum monthly increase in solar insolation, and no family history × maximum monthly increase in solar insolation.
†Dependent variable: Age of Onset. Model: intercept physicians per 1000 onset country population, maximum monthly increase in solar insolation, and first episode manic × maximum monthly increase in solar insolation.

family history of a mood disorder and with an onset of mania rather than depression. This confirmation using a larger and more diverse sample with collection and onset locations on six continents, and when only including the youngest birth-cohort, suggests that these findings are not due to chance. As with the prior studies, the maximum monthly increase in solar insolation occurred in springtime. The effect was related to the size of the maximum monthly increase, regardless if starting from a low level of solar insolation at very northern latitude, or from a medium level at a mid-latitude desert.

From a clinical perspective, physicians should recognize the potential for a younger age of onset in locations with a large increase in sunlight in springtime, and the potential for an older onset in areas with little seasonal change. The interaction with family history suggests that a genetic predisposition to bipolar disorder involves circadian dysregulation (18). The findings also emphasize the importance of obtaining a family history from all

patients, especially as the age of onset was younger in the youngest birth-cohort. Early onset bipolar disorder is associated both with family history and with poorer outcomes (54–57).

These models were different from our prior analyses due to the inclusion of physician density. Using data from such diverse countries, it is not surprising that having an important socioeconomic variable in addition to the maximum monthly increase in solar insolation improved the model for age of onset. The physician workforce directly impacts health outcomes (58, 59) and varies greatly between high- and low-income countries and within high-income regions, and especially for mental health (60, 61).

Recent and remarkable societal changes relating to light exposure may be contributing to the increased vulnerability to a springtime circadian challenge in the youngest birth-cohort and may be of particular concern for future generations. These include the conversion from incandescent to LED (light-emitting diode) lighting, the use of mobile

devices backlit with LEDs, and the rise of a 24-h society. The Nobel Prize in physics in 2014 was awarded to Isamu Akasaki, Hiroshi Amano, and Shuji Nakamura for the invention of the blue LED in the 1990s, which enabled a new method for semiconductors to create white light (62). LEDs are energy-efficient, requiring 85% less energy than incandescent light bulbs (63), and are long-lasting. Conversion to LEDs has been extremely rapid, with 69% of all light bulbs sold worldwide expected to be LEDs by 2020 (63). However, differences in the properties of LEDs may have physiological impact. Incandescent lights have a dominant wavelength of 574 nm, close to the peak sensitivity of photopic photoreception of 555 nm (64, 65). In contrast, white LEDs have a dominant wavelength of 482 nm, in the blue light range, close to the peak sensitivity for circadian photoreception (~480 nm for melanopsin and ~460 nm for melatonin suppression) (33, 64, 66).

Compared to the past, many people today experience darker days and brighter nights (28). In the daytime, people are spending more time indoors and all indoor lighting (incandescent and LED) is vastly dimmer and has a different spectral pattern than the Sun. Unlike with vision, people are not aware if they do not receive enough daytime light for circadian needs (65). In the night-time, indoor lighting is a necessity, but long-term effects of exposure to LEDs after sunset on the circadian system are unknown. Sufficient darkness during the dark phase of the light–dark cycle is needed for melatonin secretion and optimal entrainment (67). Additionally, about 80% of the world's population lives where the night sky brightness is above the threshold for light pollution (68), and high-intensity LED streetlights pose a health threat (69, 70). International lighting industry standards were optimized for vision. The complexity of non-visual physiological responses and the need to balance benefits and harmful effects pose many challenges for developing new standards (29, 70, 71). The intensity, spectrum, duration, and timing of all lighting, and prior light and dark exposure may all impact circadian entrainment (29,71–72).

Digital devices, such as smartphones, eReaders, tablets, video games, computer screens, and TV sets, are backlit with LED light to enhance the daytime brightness and contrast (73, 74). While well suited for the screen size of mobile devices, LEDs emit bright blue light. In the USA, 72% of adolescents used a cell phone in the hour before bedtime (75), and many adolescents in Belgium used a cell phone after lights out (76). Recent investigations report an association between evening use of technology (smartphones, computers,

and eReaders) and reduced melatonin secretion in healthy adults and adolescents (77–79), and decreased sleep in children and adults (75, 77, 80, 81). In a systematic review of 67 international studies of children and adolescents, increasing screen time was associated with an adverse sleep outcome (82). The heavy use of mobile technology by children and adolescents is of particular concern. Early pubertal children have increased sensitivity to evening light as measured by melatonin suppression (83), and transmission of blue light in the young is much greater than in the old due to aging of the crystalline lens and loss of pupil area (65, 84).

Daily patterns of light exposure reflect individual preferences and societal requirements (29, 35). Recently, competitiveness, consumer demand, and globalization are creating a 24-h society (85). The continuous provision of goods and services offers considerable customer convenience, but requires that many people work non-traditional and irregular work schedules, including late night and early morning. Yet people with bipolar disorder may be especially vulnerable to the circadian disruption experienced by shift workers (86, 87). The importance of regularity in daily patterns of exposure to circadian stimuli may be greatest for individuals who have suboptimal circadian function (88). The increase in irregular work schedules is occurring worldwide (89, 90), with 35% of employed persons in the USA having flexible work hours in 2012 (91).

Limitations

The process of data gathering was not standardized across all collection sites, although based on the DSM-IV criteria. Family history data were not validated and may be unreliable. There may be recall bias with self-reported age of onset in relation to episodes early in life or of less severity. The sample was not demographically representative of the country populations. However, the unadjusted mean age of onset in the sample of 25.4 ± 10.6 years was similar to that in other international studies: 25.7 years for bipolar I disorder (54) and 25.6 years for any bipolar disorder (92). Although 79% of the samples were from the Northern Hemisphere, about 87.5% of the world's population lives there (93). There was no individual data on sun exposure, sun-related behaviours, shift work, technology use, skin type, serum vitamin D levels (94), or retinal abnormalities (95, 96). There was also no individual data on perinatal light exposure, which may impact future circadian resilience (97, 98). Other functions stimulated by

blue light including direct enhancement of cognition (99) were not considered. Societal changes unrelated to light were not considered, including the tumultuous events of the twentieth century that impacted the older birth-cohorts (46). There was a downward bias in the age of onset of the youngest birth-cohort due to the absence of individuals with late onset bipolar disorder, ascertainment bias, and the potential for earlier mortality in those with early onset (48, 100, 101). Data from the Southern Hemisphere was shifted by 6 months, which discounts the cultural dimensions of seasonality. The model results show an association but cannot show causality. However, the impacts of circadian disruption on the course bipolar disorder needs to be studied, whether or not the association is causative (102).

In conclusion, a large increase in the maximum monthly solar insolation in springtime may influence the onset of bipolar disorder, especially for patients with a family history of mood disorders. The larger the maximum monthly increase in solar insolation, the younger the onset of bipolar disorder. With the youngest age of onset in the youngest birth-cohort, recent societal changes that may impact adaptability to a circadian challenge need investigation. These include LED lighting, mobile technology backlit with LEDs, and 24-h lifestyles. While country conditions such as physician density are beyond the individual's ability to control, individual behaviour directly impacts light exposure and darkness at night. Perhaps, treatment recommendations for bipolar disorder may include optimum daytime and night-time light exposure, including from technology.

Acknowledgements

Declarations of interest

The authors declare that they have no conflict of interests.

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