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Michael Bauer [a,*], Tasha Glenn [b], Eric D. Achtyes [c,d], Martin Alda [e], Esen Agaoglu [f], Kürşat Altınbaş [g], Ole A. Andreassen [h], Elias Angelopoulos [i], Raffaella Ardau [j], Memduha Aydin [k], Yavuz Ayhan [f], Christopher Baethge [l], Rita Bauer [a], Bernhard T. Baune [m,n,o], Ceylan Balaban [p], Claudia Becerra-Palars [q], Aniruddh P. Behere [r], Prakash B. Behere [s], Habte Belete [t], Tilahun Belete [t], Gabriel Okawa Belizario [u], Frank Bellivier [v], Robert H. Belmaker [w], Francesco Benedetti [x,y], Michael Berk [z,aa], Yuly Bersudsky [ab], Şule Bicakci [f,ac], Harriet Birabwa-Oketcho [ad], Thomas D. Bjella [h], Conan Brady [ae], Jorge Cabrera [af], Marco Cappucciati [ag], Angela Marianne Paredes Castro [z], Wei-Ling Chen [ah], Eric Y.W. Cheung [ai], Silvia Chiesa [ag], Marie Crowe [aj], Alessandro Cuomo [ak], Sara Dallaspezia [y], Maria Del Zompo [j], Pratikkumar Desai [d], Seetal Dodd [z,al], Bruno Etain [v], Andrea Fagiolini [ak], Frederike T. Fellendorf [am], Ewa Ferensztajn-Rochowiak [an], Jess G. Fiedorowicz [ao], Kostas N. Fountoulakis [ap], Mark A. Frye [aq], Pierre A. Geoffroy [ar,as,at], Ana Gonzalez-Pinto [au], John F. Gottlieb [av], Paul Grof [aw], Bartholomeus C.M. Haarman [ax], Hirohiko Harima [ay], Mathias Hasse-Sousa [az], Chantal Henry [ba], Lone Høffding [bb], Josselin Houenou [bc,bd], Massimiliano Imbesi [ag], Erkki T. Isometsä [be,bf], Maja Ivkovic [bg], Sven Janno [bh], Simon Johnsen [bi], Flávio Kapczinski [az], Gregory N. Karakatsoulis [ap], Mathias Kardell [bj], Lars Vedel Kessing [bk], Seong Jae Kim [bl], Barbara König [bm], Timur L. Kot [bn], Michael Koval [bo], Mauricio Kunz [az], Beny Lafer [u], Mikael Landén [bj,bp], Erik R. Larsen [bq], Melanie Lenger [am], Ute Lewitzka [a], Rasmus W. Licht [br,bs], Carlos Lopez-Jaramillo [bt], Alan MacKenzie [bu], Helle Østergaard Madsen [bv], Simone Alberte Kongstad A. Madsen [bi], Jayant Mahadevan [bw], Agustine Mahardika [bx], Mirko Manchia [by,bz,ca], Wendy Marsh [cb], Monica Martinez-Cengotitabengoa [cc,dt], Klaus Martiny [bv], Yuki Mashima [cd], Declan M. McLoughlin [ce], Ybe Meesters [ax], Ingrid Melle [h], Fátima Meza-Urzúa [cf], Yee Ming Mok [cg], Scott Monteith [ch], Muthukumaran Moorthy [bw], Gunnar Morken [ci,cj], Enrica Mosca [j], Anton A. Mozzhegorov [ck], Rodrigo Munoz [cl], Starlin V. Mythri [cm], Fethi Nacef [cn], Ravi K. Nadella [bw], Takako Nakanotani [co], René Ernst Nielsen [br,bs], Claire O'Donovan [e], Adel Omrani [cp], Yamima Osher [ab], Uta Ouali [cn], Maja Pantovic-Stefanovic [bg], Pornjira Pariwatcharakul [cq], Joanne Petite [e], Andrea Pfennig [a], Yolanda Pica Ruiz [cr], Marco Pinna [bz,cs], Maurizio Pompili [ct], Richard Porter [aj], Danilo Quiroz [cu], Francisco Diego Rabelo-da-Ponte [cv], Raj Ramesar [cw], Natalie Rasgon [cx], Woraphat Ratta-apha [cq], Michaela Ratzenhofer [am], Maria Redahan [ae], M.S. Reddy [cy], Andreas Reif [p], Eva Z. Reininghaus [am], Jenny Gringer Richards [cz], Philipp Ritter [a], Janusz K. Rybakowski [an], Leela Sathyaputri [cz], Ângela M. Scippa [da], Christian Simhandl [db], Daniel Smith [dc], José Smith [dd], Paul W. Stackhouse Jr. [de], Dan J. Stein [df], Kellen Stilwell [d], Sergio Strejilevich [dd], Kuan-Pin Su [dg,dh], Mythily Subramaniam [di], Ahmad Hatim Sulaiman [dj], Kirsi Suominen [dk], Andi J. Tanra [dl], Yoshitaka Tatebayashi [co], Wen Lin Teh [di], Leonardo Tondo [dm,dn],

* Corresponding author.
  E-mail address: michael.bauer@ukdd.de (M. Bauer).

Carla Torrent [do], Daniel Tuinstra [d], Takahito Uchida [cd,dp], Arne E. Vaaler [ci,cj], Eduard Vieta [do], Biju Viswanath [bw], Maria Yoldi-Negrete [dq], Oguz Kaan Yalcinkaya [f], Allan H. Young [dr], Yosra Zgueb [cn], Peter C. Whybrow [ds]

[a] Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Faculty of Medicine, Technische Universität Dresden, Dresden, Germany
[b] ChronoRecord Association, Fullerton, CA, USA
[c] Michigan State University College of Human Medicine, Division of Psychiatry & Behavioral Medicine, Grand Rapids, MI, USA
[d] Pine Rest Christian Mental Health Services, Grand Rapids, MI, USA
[e] Department of Psychiatry, Dalhousie University, Halifax, NS, Canada
[f] Department of Psychiatry, Hacettepe University Faculty of Medicine, Ankara, Turkey
[g] Department of Psychiatry, Selcuk University Faculty of Medicine, Mazhar Osman Mood Center, Konya, Turkey
[h] NORMENT Centre, Division of Mental Health and Addiction, Oslo University Hospital & Institute of Clinical Medicine, University of Oslo, Oslo, Norway
[i] Department of Psychiatry, National and Capodistrian University of Athens, Medical School, Eginition Hospital, Athens, Greece
[j] Section of Neurosciences and Clinical Pharmacology, Department of Biomedical Sciences, University of Cagliari, Sardinia, Italy
[k] Department of Psychiatry, Selcuk University Faculty of Medicine, Konya, Turkey
[l] Department of Psychiatry and Psychotherapy, University of Cologne Medical School, Cologne, Germany
[m] Department of Psychiatry, University of Münster, Münster, Germany
[n] Department of Psychiatry, Melbourne Medical School, The University of Melbourne, Melbourne, Australia
[o] The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Parkville, VIC, Australia
[p] Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt, Johann Wolfgang Goethe-Universität Frankfurt am Main, Frankfurt am Main, Germany
[q] National Institute of Psychiatry '"Ramón de la Fuente Muñiz", Mexico City, Mexico
[r] Department of Pediatrics and Human Development, Michigan State University, Grand Rapids, MI, USA
[s] Department of Psychiatry, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences (Deemed University), Wardha, India
[t] Department of Psychiatry, College of Medicine and Health Sciences, Bahir Dar University, Bahir Dar, Ethiopia
[u] Bipolar Disorder Research Program, Department of Psychiatry, University of São Paulo Medical School, São Paulo, Brazil
[v] Département de Psychiatrie et de Médecine Addictologique, Assistance Publique – Hôpitaux de Paris, INSERM UMR-S1144, Université de Paris, FondaMental Foundation, Paris, France
[w] Professor Emeritus of Psychiatry, Ben Gurion University of the Negev, Beer Sheva, Israel
[x] University Vita-Salute San Raffaele, Milan, Italy
[y] Psychiatry & Clinical Psychobiology, Division of Neuroscience, San Raffaele Scientific Institute, Milan, Italy
[z] Deakin University, IMPACT – the Institute for Mental and Physical Health and Clinical Translation, School of Medicine, Barwon Health, Geelong, Australia
[aa] Orygen, The National Centre of Excellence in Youth Mental Health, Centre for Youth Mental Health, Florey Institute for Neuroscience and Mental Health and the Department of Psychiatry, The University of Melbourne, Melbourne, Australia
[ab] Department of Psychiatry, Faculty of Health Sciences, Beer Sheva Mental Health Center, Ben Gurion University of the Negev, Beer Sheva, Israel
[ac] Department of Psychiatry, Baskent University Faculty of Medicine, Ankara, Turkey
[ad] Butabika Hospital, Kampala, Uganda
[ae] Department of Psychiatry, Trinity College Dublin, St Patrick's University Hospital, Dublin, Ireland
[af] Mood Disorders Clinic, Dr. Jose Horwitz Psychiatric Institute, Santiago de Chile, Chile
[ag] Department of Mental Health and Substance Abuse, Piacenza, Italy
[ah] Department of Psychiatry, Chiayi Branch, Taichung Veterans General Hospital, Chiayi, Taiwan
[ai] Private practice, Central, Hong Kong
[aj] Department of Psychological Medicine, University of Otago, Christchurch, New Zealand
[ak] Department of Molecular Medicine, University of Siena School of Medicine, Siena, Italy
[al] Department of Psychiatry, University of Melbourne, Parkville, Victoria, Australia
[am] Department of Psychiatry and Psychotherapeutic Medicine, Medical University Graz, Graz, Austria
[an] Department of Adult Psychiatry, Poznan University of Medical Sciences, Poznan, Poland
[ao] Department of Psychiatry, School of Epidemiology and Public Health, University of Ottawa, Ottawa, ON, Canada
[ap] 3rd Department of Psychiatry, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece
[aq] Department of Psychiatry & Psychology, Mayo Clinic Depression Center, Mayo Clinic, Rochester, MN, USA
[ar] Département de psychiatrie et d'addictologie, AP-HP, GHU Paris Nord, DMU Neurosciences, Hopital Bichat - Claude Bernard, F-75018 Paris, France
[as] GHU Paris - Psychiatry & Neurosciences, 1 rue Cabanis, 75014 Paris, France
[at] Université de Paris, NeuroDiderot, Inserm, FHU I2-D2, F-75019 Paris, France
[au] BIOARABA. Department of Psychiatry, University Hospital of Alava, University of the Basque Country, CIBERSAM, Vitoria, Spain
[av] Department of Psychiatry, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA
[aw] Mood Disorders Center of Ottawa and the Department of Psychiatry, University of Toronto, Canada
[ax] Department of Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, Netherlands
[ay] Department of Psychiatry, Tokyo Metropolitan Matsuzawa Hospital, Setagaya, Tokyo, Japan
[az] Department of Psychiatry, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil
[ba] Department of Psychiatry, GHU Paris Psychiatrie & Neurosciences, F-75014, Paris France, Université de Paris, F-75006 Paris, France
[bb] Department of Clinical Research, University of Southern Denmark, Odense, Denmark
[bc] Université Paris Est Créteil, INSERM, IMRB, Translational Neuropsychiatry, APHP, Mondor Univ Hospitals, Fondation FondaMental, F-94010 Créteil, France
[bd] Université Paris Saclay, CEA, Neurospin, F-91191 Gif-sur-Yvette, France
[be] Department of Psychiatry, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
[bf] National Institute for Health and Welfare, Helsinki, Finland
[bg] University Clinical Center of Serbia, Clinic for Psychiatry, Belgrade, Serbia
[bh] Department of Psychiatry, University of Tartu, Tartu, Estonia
[bi] Unit for Psychiatric Research, Aalborg University Hospital, Aalborg, Denmark
[bj] Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
[bk] Copenhagen Affective Disorder Research Center (CADIC), Psychiatric Center Copenhagen, Rigshospitalet, Copenhagen, Denmark
[bl] Department of Psychiatry, Chosun University School of Medicine, Gwangju, Republic of Korea
[bm] BIPOLAR Zentrum Wiener Neustadt, Wiener Neustadt, Austria
[bn] Khanty-Mansiysk Clinical Psychoneurological Hospital, Khanty-Mansiysk, Russia
[bo] Department of Neuroscience, Michigan State University, East Lansing, MI, USA
[bp] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
[bq] Mental Health Department Odense, University Clinic and Department of Regional Health Research, University of Southern Denmark, Esbjerg, Denmark
[br] Psychiatry – Aalborg University Hospital, Aalborg, Denmark
[bs] Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

[bt] Mood Disorders Program, Hospital Universitario San Vicente Fundación, Research Group in Psychiatry, Department of Psychiatry, Faculty of Medicine, Universidad de Antioquia, Medellín, Colombia

[bu] Forensic Psychiatry, University of Glasgow, NHS Greater Glasgow and Clyde, Glasgow, UK

[bv] Copenhagen University Hospitals, Psychiatric Centre Copenhagen, Copenhagen, Denmark

[bw] Department of Psychiatry, National Institute of Mental Health and Neuro Sciences (NIMHANS), Bengaluru, India

[bx] Department of Psychiatry, Faculty of Medicine, Mataram University, Mataram, Indonesia

[by] Department of Pharmacology, Dalhousie University, Halifax, Nova Scotia, Canada

[bz] Section of Psychiatry, Department of Medical Science and Public Health, University of Cagliari, Cagliari, Italy

[ca] Unit of Clinical Psychiatry, University Hospital Agency of Cagliari, Cagliari, Italy

[cb] Department of Psychiatry, University of Massachusetts Medical School, Worcester, MA, USA

[cc] Osakidetza, Basque Health Service, BioAraba Health Research Institute, University of the Basque Country, Spain

[cd] Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan

[ce] Dept of Psychiatry & Trinity College Institute of Neuroscience, Trinity College Dublin, St Patrick's University Hospital, Dublin, Ireland

[cf] Department of Child and Adolescent Psychiatry und Psychotherapy, SHG Klinikum, Idar-Oberstein, Germany

[cg] Department of Mood and Anxiety disorders, Institute of Mental Health, Singapore City, Singapore

[ch] Michigan State University College of Human Medicine, Traverse City Campus, Traverse City, MI, USA

[ci] Department of Mental Health, Norwegian University of Science and Technology – NTNU, Trondheim, Norway

[cj] Department of Psychiatry, St Olavs' University Hospital, Trondheim, Norway

[ck] Soviet Psychoneurological Hospital, Urai, Russia

[cl] Department of Psychiatry, University of California San Diego, San Diego, CA, USA

[cm] Makunda Christian Leprosy and General Hospital, Bazaricherra, Assam 788727, India

[cn] Razi Hospital, Faculty of Medicine, University of Tunis-El Manar, Tunis, Tunisia

[co] Affective Disorders Research Project, Tokyo Metropolitan Institute of Medical Science, Setagaya, Tokyo, Japan.

[cp] Tunisian Bipolar Forum, Érable Médical Cabinet 324, Lac 2, Tunis, Tunisia

[cq] Department of Psychiatry, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

[cr] Hospital "Ángeles del Pedregal", Mexico City, Mexico

[cs] Lucio Bini Mood Disorder Center, Cagliari, Italy

[ct] Department of Neurosciences, Mental Health and Sensory Organs, Sant'Andrea Hospital, Sapienza University of Rome, Rome, Italy

[cu] Deparment of Psychiatry, Diego Portales University, Santiago de Chile, Chile

[cv] University of Central Lancashire, School of Pharmacy and Biomedical Sciences, Preston, Lancashire, United Kingdom

[cw] SA MRC Genomic and Precision Medicine Research Unit, Division of Human Genetics, Department of Pathology, Institute of Infectious Diseases and Molecular Medicine, University of Cape Town, South Africa

[cx] Department of Psychiatry and Behavioral Sciences, Stanford School of Medicine, Palo Alto, CA, USA

[cy] Asha Bipolar Clinic, Asha Hospital, Hyderabad, Telangana, India

[cz] Departments of Psychiatry, Epidemiology, and Internal Medicine, Iowa Neuroscience Institute, The University of Iowa, Iowa City, IA, USA

[da] Department of Neuroscience and Mental Health, Federal University of Bahia, Salvador, Brazil

[db] Bipolar Zentrum Wiener Neustadt, Sigmund Freud Privat Universität, Vienna, Austria

[dc] Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, Scotland, UK

[dd] AREA, Assistance and Research in Affective Disorders, Buenos Aires, Argentina.

[de] Science Directorate/Climate Science Branch, NASA Langley Research Center, Hampton, VA, USA

[df] Department of Psychiatry, MRC Unit on Risk & Resilience in Mental Disorders, University of Cape Town, Cape Town, South Africa

[dg] College of Medicine, China Medical University (CMU), Taichung, Taiwan

[dh] An-Nan Hospital, China Medical University, Tainan, Taiwan

[di] Research Division, Institute of Mental Health, Singapore

[dj] Department of Psychological Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

[dk] Department of Social Services and Health Care, Psychiatry, City of Helsinki, Helsinki, Finland

[dl] Department of Psychiatry, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

[dm] McLean Hospital-Harvard Medical School, Boston, MA, USA

[dn] Mood Disorder Lucio Bini Centers, Cagliari e Roma, Italy

[do] Clinical Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia, Spain

[dp] Melbourne Neuropsychiatry Centre, Department of Psychiatry, The University of Melbourne, Melbourne, Australia

[dq] Subdirección de Investigaciones Clínicas. Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz, Mexico City, Mexico.

[dr] Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

[ds] Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles (UCLA), Los Angeles, CA, USA

[dt] The Psychology Clinic of East Anglia, Norwich, United Kingdom

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ABSTRACT

Objective: Circadian rhythm disruption is commonly observed in bipolar disorder (BD). Daylight is the most powerful signal to entrain the human circadian clock system. This exploratory study investigated if solar insolation at the onset location was associated with the polarity of the first episode of BD I. Solar insolation is the amount of electromagnetic energy from the Sun striking a surface area of the Earth.

Methods: Data from 7488 patients with BD I were collected at 75 sites in 42 countries. The first episode occurred at 591 onset locations in 67 countries at a wide range of latitudes in both hemispheres. Solar insolation values were obtained for every onset location, and the ratio of the minimum mean monthly insolation to the maximum mean monthly insolation was calculated. This ratio is largest near the equator (with little change in solar insolation over the year), and smallest near the poles (where winter insolation is very small compared to summer insolation). This ratio also applies to tropical locations which may have a cloudy wet and clear dry season, rather than winter and summer.

Results: The larger the change in solar insolation throughout the year (smaller the ratio between the minimum monthly and maximum monthly values), the greater the likelihood the first episode polarity was depression. Other associated variables were being female and increasing percentage of gross domestic product spent on country health expenditures. (All coefficients: $P \leq 0.001$).

Conclusion: Increased awareness and research into circadian dysfunction throughout the course of BD is warranted.

1. Introduction

The functions of the circadian clock system are fundamental to human health, and disruptions to circadian rhythms contribute to a wide range of diseases [1–3]. Alterations in circadian rhythms across the lifespan are associated with psychiatric disorders including mood disorders, schizophrenia, anxiety disorders [4–8], and neurodegenerative diseases [9,10]. Patients with bipolar disorder (BD) exhibit symptoms of circadian disruption, such as sleep disturbances, social rhythm alterations and endocrine abnormalities, and these symptoms may persist during remission [11–15]. The consequences of circadian dysfunction in BD may both trigger and exacerbate episodes [16,17]. Dysfunction of circadian clocks may also contribute to the metabolic comorbidity frequently present in patients with psychiatric disorders [18,19].

The human circadian clock system is entrained to the Earth's 24 h rotation using signals from the environment, where daylight is the most powerful signal [20–23]. Daylight has fundamental and extensive effects on the circadian system governing daily human physiology and behavior, including alertness, sleep, mood, stress, cognition, and regulation of neuroendocrine, cardiovascular, and metabolic functions [20,24–30]. Daylight impacts humans through three main routes: vision, skin absorption triggering vitamin D production, and the non-visual responses to light in the retina that drive the circadian clock system. Solar insolation (incoming solar radiation) is defined as the amount of electromagnetic energy from the Sun striking a surface area of the Earth [31]. We previously found a strong, inverse relation between the maximum monthly increase in solar insolation in springtime and the age of onset of BD I [32]. The purpose of this exploratory study was to determine if solar insolation was associated with the polarity of the first episode of BD I, using a large global sample of patient data. The polarity of the first episode affects the time delay to receive a diagnosis of BD [33–36], and has clinically relevant prognostic information [37–41].

2. Methods

2.1. Data collection

Researchers at university medical centers and specialty clinics, as well as individual practitioners, obtained data retrospectively using direct questioning, record review, or both. All patients included in the study had a clinical diagnosis of BD from a psychiatrist according to DSM-IV or DSM-5 criteria. Data were collected between 2010 and 2016 and 2019–2021. Study approval was obtained from local institutional review boards, following local requirements. Participants signed the informed consent before data analysis for this study was initiated. Details about the project methodology were published previously [32,42–44].

2.2. Data collection sites

There were 75 collection sites in 42 countries as shown in Fig. 1. Collection sites located in the northern hemisphere were: Aalborg, Denmark; Aarhus, Denmark; Ankara, Turkey; Athens, Greece; Bangkok, Thailand; Barcelona, Spain; Barhir Dar, Ethiopia; Beer Sheva, Israel; Belgrade, Serbia; Bengaluru, India; Cagliari, Sardinia, Italy (2 sites); Calgary, Canada; Copenhagen, Denmark; Dresden, Germany; Dublin, Ireland; Frankfurt, Germany; Halifax, Canada; Helsinki, Finland; Glasgow, UK; Gothenburg, Sweden; Grand Rapids, MI, USA; Graz, Austria; Groningen, Netherlands; Hong Kong, China; Hyderabad, India; Iowa City, Iowa, USA; Jincheon, South Korea; Kampala, Uganda; Kansas City, KS, USA; Khanti-Mansiysk, Russia; Konya, Turkey; Kuala Lumpur, Malaysia; Los Angeles, CA, USA; Medellín, Colombia; Mexico City, Mexico; Milan, Italy; Oslo, Norway; Ottawa, Canada; Piacenza, Italy; Palo Alto, CA, USA; Paris, France (2 sites); Poznan, Poland; Rochester, MN, USA; Rome, Italy; San Diego, CA, USA; Siena, Italy; Singapore; Stockholm, Sweden; Tartu, Estonia; Thessaloniki, Greece (2 sites); Tokyo, Japan (3 sites); Taichung, Taiwan; Trondheim, Norway; Tunis, Tunisia; Vitoria, Spain; Wardha, India; Wiener Neustadt, Austria; Worcester, MA, USA, and Würzburg, Germany. Collection sites located in the southern hemisphere were: Adelaide, Australia; Melbourne/ Geelong, Australia; Buenos Aires, Argentina; Cape Town, South Africa; Christchurch, New Zealand; Mataram, Indonesia; Porto Alegre, Brazil; Salvador, Brazil; Santiago, Chile (2 sites); and São Paulo, Brazil.

2.3. Patient and country data

Data collected for each patient were sex, age of onset, polarity of first episode, family history of mood disorders, history of psychosis, episode course, history of alcohol and substance abuse, and history of suicide attempts. For each patient, three locations were also collected: birth
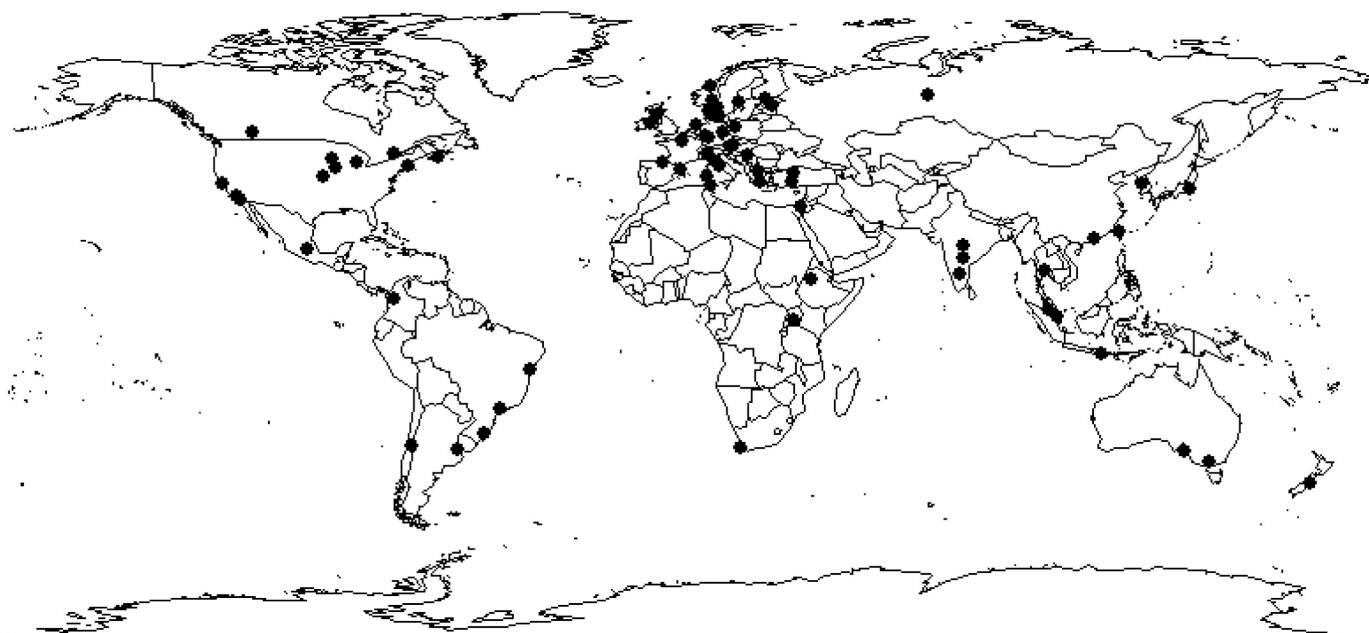

Fig. 1. Location of the 75 international collection sites in 42 countries.

location, onset location and current location.

A variety of country specific socioeconomic data were obtained for all onset locations: physician density per 1000 population, country median age, unemployment rate, poverty rate, gross domestic product (GDP) per capita [45], health expenditure as a percentage of GDP [46], psychiatrists per 100,000 [47], Gini index of income inequality [48], and the gender inequality index [49].

2.4. Solar insolation

The solar insolation values were obtained from the NASA POWER database version 8.0.1, which provides average monthly solar insolation expressed in kilowatt hours/square meter/day (kWh/m^2/day) based on satellite observations collected between 1983 and the present [31]. A 22-year climatology of insolation spanning Jan 1984 - December 2013 at spatial resolution of 1° x 1° latitude/longitude was obtained. The actual patient onset locations were grouped into reference onset locations representing all onset locations within a 1° x 1° grid of latitude and longitude. For each patient, the latitude and longitude of the reference onset location were used to obtain the solar insolation values.

The mean monthly solar insolation received at different latitudes changes throughout the year, with very little change near the equator and extreme changes near the north and south poles. Solar insolation values for locations at the same latitude may also vary considerably due to local conditions such as cloud cover, aerosols (including dust and pollution), water vapor amounts, and altitude. The variance in solar insolation across the year is often considered in terms of changes between the winter months and summer months. However, locations in the tropics (<23.5° north or south of the equator), may have a wet season where clouds reduce solar insolation and a dry season with clear skies rather than a winter/summer insolation pattern. Therefore, to capture the range of solar insolation in tropical as well as non-tropical areas, the ratio of the minimum mean monthly insolation to the maximum mean monthly insolation was created to summarize the changes in solar insolation throughout the year at each reference onset location.

2.5. Statistics

The generalized estimating equations (GEE) statistical technique was used to account for both the correlated data and unbalanced number of patients at reference onset locations. The GEE technique estimates the dependent variable as a function of the entire population, producing a population averaged or marginal estimates of model coefficients [50]. All GEE models in this study were estimated using a binomial distribution, an exchangeable working correlation matrix and a logit link function where the polarity of the first episode (depressed or manic/hypomanic) was the dependent binary variable. To identify the best model, the multivariate model estimates were compared using the corrected quasi-likelihood independence model criterion [51] and confidence intervals at the 0.01 significance level to reduce the chance of type 1 errors. Based on the logit link function, the exponentiated coefficient can be interpreted as the effect size [52]. Demographic variables were reported using descriptive statistics. SPSS version 26.0 was used for all analyses. The R software was used to create Fig. 1 [53].

3. Results

Data were available for 11,063 patients with BD, of which 8080 had a diagnosis of BD I. Of the 8080 patients, 7488 (92.7%) had all the variables in the best model and were included in the analysis. The demographics of the 7488 patients are shown in Table 1. Of the 7488 patients, 4366 (58.3%) were female, and the polarity of the first episode

Table 1
Demographics of patients with BD I[1] (*N* = 7488).

Parameter	Value	N	%
Sex			
	Female	4366	58.3
	Male	3122	41.7
Polarity of first episode			
	Manic/Hypomanic	3745	50.0
	Depressed	3743	50.0
Family history of mood disorder			
	No	3179	47.7
	Yes	3492	52.3
Alcohol or substance abuse			
	No	3677	69.1
	Yes	1645	30.9
History of psychosis			
	No	2146	35.7
	Yes	3859	64.3
Comorbid anxiety/panic/ OCD			
	No	4017	76.6
	Yes	995	23.4
Parameter	Value	Mean	SD
Health expenditures as percent of country GDP		8.6	2.7
Age of onset		25.5	10.5

[1] Missing values excluded.

was depressed for 3743 (50%). The mean age of onset for the 7488 patients was 25.6 ± 10.7 years, similar to other international studies [54–56]. For the 7488 patients, there were 591 reference onset locations in 67 countries at a wide range of latitudes in both hemispheres. The average number of patients at each onset location was 12.7, with 285 onset locations having a single patient. Of the 7488 patients, 1685 (22.5%) had an onset location in the tropics, and 1576 (21%) had an onset location in the southern hemisphere.

3.1. Model estimate

The best fitting model estimated the percentage of patients with a first episode of depression using an intercept, the ratio of the minimum mean monthly insolation to the maximum mean monthly insolation for the reference onset location, sex, and the country health expenditure as a percentage of GDP. See Table 2. The estimated coefficients for the best model suggest that the odds of first episode of depression decrease by 6.7% for every 0.1 increase in the ratio of minimum mean monthly insolation to maximum mean monthly insolation. Alternatively stated, comparing a ratio of 1 (near the equator) to a ratio of 0 (near a pole), there was a 67% difference in the odds of a first episode of depression with the lowest odds at the equator. The model estimates that being female will increase the odds of a first episode of depression by 47% and a 1% increase in country health expenditure as a percentage of GDP will increase the odds of a first episode of depression by 7%. The best model included 92.7% of the collected data.

The ratio of the minimum mean monthly insolation to the maximum mean monthly insolation, solar insolation varied between the extremes of 0.0 near the north pole and 0.89 near the equator. See Table 3. The current health expenditure as a percentage of GDP for the year 2018 varied between the extremes of 2.9% and 16.9% of GDP. The other patient variables, solar insolation variables and country variables considered were not significant or the models were not as meaningful.

Table 2

Estimated parameters explaining the polarity of the first episode for patients with BD I (N = 7488)[1].

Parameters	Coefficient estimate (β)	Standard Error	Exp (β)	99% Confidence Interval		Coefficient Significance	
				Lower	Upper	Wald Chi-squared	P
Intercept	−0.646	0.1885	0.524	−1.016	−0.277	11.745	0.001
Ratio of monthly mean minimum/monthly mean maximum insolation	−1.109	0.2803	0.330	−1.658	−0.559	15.645	< 0.001
Sex - Female	0.338	0.0540	1.474	0.282	0.494	51.618	< 0.001
Country health expenditure as percentage of GDP	0.075	0.0146	1.077	0.046	0.103	25.945	< 0.001

[1] Dependent variable: Polarity of first episode depressed (yes/no). Model: intercept, ratio of monthly mean minimum/monthly mean maximum insolation at onset location, female (yes/no), country health expenditure as percentage of GDP.

Table 3

Ratio of monthly mean minimum/monthly mean maximum insolation: example onset locations by latitude group.

Degrees Latitude North + South	Onset Location	Ratio of Monthly Mean Minimum/Monthly Mean Maximum Insolation
0--9	Kampala, Uganda	0.8197
	Kuala Lumpur, Malaysia	0.7694
	Mataram, Indonesia	0.7831
	Medellín, Columbia	0.8370
	Singapore	0.7797
10--19	Bahir Dar, Ethiopia	0.7713
	Bangkok, Thailand	0.7207
	Bengaluru, India	0.6814
	Hyderabad, India	0.6421
	Mexico City, Mexico	0.6855
	Salvador, Brazil	0.6246
20--29	Hong Kong, China	0.6016
	São Paulo, Brazil	0.6050
	Taichung, Taiwan	0.3931
	Wardha, India	0.5750
30--39	Ankara, Turkey	0.2374
	Athens, Greece	0.2319
	Beer Sheva, Israel	0.3556
	Buenos Aires, Argentina	0.3149
	Cagliari, Italy	0.2328
	Cape Town, South Africa	0.3227
	Los Angeles, CA, USA	0.3503
	Melbourne, Australia	0.2913
	San Francisco, CA, USA	0.3137
	Santiago, Chile	0.2879
	Seoul, South Korea	0.4404
	Tokyo, Japan	0.5574
	Tunis, Tunisia	0.2859
40--49	Belgrade, Serbia	0.1960
	Barcelona, Spain	0.2603
	Boston, MA, USA	0.2662
	Christchurch, New Zealand	0.2461
	Grand Rapids, MI, USA	0.2256
	Halifax, Canada	0.2270
	Minneapolis, MN, USA	0.2371
	Paris, France	0.1540
	Rome, Italy	0.2203
	Siena, Italy	0.2077
	Vienna, Austria	0.1667
	Würzburg, Germany	0.1477
50--59	Aarhus, Denmark	0.0782
	Calgary, Canada	0.1454
	Dresden, Germany	0.1379
	Dublin, Ireland	0.1149
	Oslo, Norway	0.0433
	Poznan, Poland	0.1290
	Stockholm, Sweden	0.0427
	Tartu, Estonia	0.0562
60+	Helsinki, Finland	0.0359
	Khanti-Mansiysk, Russia	0.0243
	Trondheim, Norway	0.0116

4. Discussion

The primary finding of this study was that increasing change in solar insolation during the year was associated with a first episode of depression in patients with BD I. The larger the change in solar insolation throughout the year at the onset location, the greater the likelihood that the polarity of the first episode was depressed. For patients living outside the tropics, the largest change in solar insolation is between winter and summer, with extreme change near the poles. For those living in the tropics, the largest change is between the wet and dry season. Approximately 20% of those with major depressive episodes will develop the defining manic or hypomanic episodes of BD, although estimates vary widely [57–59]. Hypothetically, this study suggests that solar insolation could be an environmental factor associated with the transition from major depressive disorder (MDD) to BD. When treating patients with a first episode of depression, physicians in locations with a large change in solar insolation across the year should monitor even more carefully for BD.

The human circadian clock system is organized in a hierarchical manner with a master clock in the suprachiasmatic nuclei (SCN) of the hypothalamus that coordinates with the peripheral clocks found in virtually all tissues and cells [1,60,61]. The master clock is entrained to the environment primarily by light changes perceived in the retina and sent to the SCN, which coordinates the circadian activities of other brain areas and the peripheral clocks using neural and neuroendocrine signals. The effects of light are related to the spectral properties, timing, duration and pattern of light exposure, and individual characteristics including age, sex, genetics, ocular health, general health, and lifestyles [20,21,28,62]. Disruptions in circadian rhythms can be defined as misalignment in biological timing between different levels of the circadian clock system, or as misalignment with the environmental light/dark cycle [63,64]. Many symptoms of circadian rhythm disruption are documented in BD, including irregular sleep-wake cycles, abnormal melatonin secretion, evening chronotype, supersensitivity to phase delaying effects of light, metabolic dysregulation, and irregular social rhythms [11,12,15,65,66]. Circadian rhythm disruption may result in mitochondrial dysfunction and contribute to the pathogenesis of BD [67,68]. Circadian rhythm disruption may also contribute to the high rate of comorbid substance use disorders reported in international studies [69,70], and substance use in turn induces changes in circadian rhythms that may exacerbate addiction [71–73]. In a sample with data from 193 countries, fewer hours of sunlight and colder weather were associated with increased alcohol consumption and alcoholic cirrhosis [74]. In prior analysis of this sample, a larger change in solar insolation across the year was associated with an increasing risk of suicide attempts [44,75].

In this study, females were at increased risk for a first episode of depression, which is consistent with some prior research [38,39,76,77]. However, review articles addressing the identification of individual risk factors associated with transition from unipolar to BD, such as family history, sex, and early age of onset, report only limited agreement among studies [58,78,79]. There are difficult clinical challenges in assessing if a first episode of depression is due to BD rather than MDD [33,80–82]. Many patients with BD are initially diagnosed with MDD, often with a 6–10 year delay before the correct diagnosis is determined and optimal treatment is started [36,83–85]. There is widespread agreement on the need to improve recognition of those at-risk for BD,

with approaches to include neuroimaging and genetic studies [33,82,86]. Differences in symptoms of circadian rhythm dysfunction may also help to differentiate between MDD and BD, with more severe symptoms of circadian dysfunction generally associated with BD [15,87,88]. Individual differences in chronobiological characteristics may also contribute to the heterogeneity in clinical presentation across the bipolar spectrum [89]. The results of this study suggest a need to increase routine awareness of circadian dysfunction.

Another finding in this study was that an increasing percentage of GDP spent on country health expenditures was associated with increasing risk of a first episode of depression. Given that depression is not a disease of affluence [90], we assume that some patients with depression remain undiagnosed and untreated in countries with less funding available for mental healthcare [91,92]. Other socioeconomic conditions and aspects of modern lifestyles may lead to circadian disruption. Many employees have unpredictable work schedules that include shift work, rotating shifts, and variable hours on short notice [93,94], situations that may cause circadian misalignment [95]. In the US, in a nationally representative survey of early career workers in hourly jobs, 41% learned their work hours one week in advance or less [96]. Another important societal change is the worldwide conversion to light-emitting diodes (LED) technology as the dominant lighting source for indoor and outdoor general illumination, and to backlight digital technology. LED lighting directly affects the non-visual response to light in the retina, and may cause circadian rhythm disruption [97–100]. Studies of children and adolescents find a high use of digital devices before bedtime, which is associated with negative effects on sleep timing and quality [101,102]. In a nationally representative study of adolescents in the US, increasing levels of artificial light at night were associated with less favorable sleep patterns, and with mood and anxiety disorders [103]. Young adults may be more vulnerable to the effects of sleep loss and circadian disruption than older adults [104]. Outdoor light pollution at night from high intensity LED streetlights may also cause circadian disruptions [105].

The results of this study highlight the need to better understand the role of circadian dysfunction in BD. Knowledge of chronobiology is growing rapidly, but the systems are very complex, such as the non-visual retinal functions and underlying genetics [62,106–108]. Additionally, there is considerable individual variation in the major measurements used in chronobiology [62,63,109]. Examples include a normal distribution of chronotypes across a population [110], and a 50-fold range in sensitivity to evening light measured by melatonin suppression across healthy young adults [111]. Increased knowledge of circadian entrainment in real world settings involving both daylight and LED lighting is also needed [26,62,106], and will help to clarify circadian dysfunction throughout the course of BD.

4.1. Limitations

There are limitations to this exploratory analysis. A seasonal analysis was not completed due to the inclusion of both tropical and non-tropical locations in the dataset. In other research, a seasonal pattern was found in about one-fourth of patients with BD, occurring more frequently in BD II [112,113]. Although the diagnosis was based on the DSM-IV or DSM-5 criteria, the process of data gathering was not standardized across collection sites. To maximize participation in the project, only minimal clinical data were collected for each patient. The length of time for a patient to receive the diagnosis of BD, or if a patient initially received an incorrect diagnosis were not available. There may be recall bias in self-reported episode polarity, especially if undiagnosed, untreated, and in early life. Episodes with mixed features were not analyzed separately. This study includes only patients with BD, and cannot estimate the rate of transition from MDD. There was also no individual data on lifestyles including shift work, sun exposure, sun related activities, technology use, or retinal abnormalities. There was large variation in the number of reference onset locations from the collection sites, related to country size, migration

patterns, and cultural factors. Cross-cultural differences in the expression of depressive symptoms and societal responses were not considered [114,115]. The sample was not demographically representative of the country populations. In this study 21% of the patients had an onset in the southern hemisphere, but it is estimated that about 12.5% of the world's population lives in the southern hemisphere [116]. Outdoor artificial light at night was not evaluated [117]. Perinatal light exposure may influence future circadian resilience, but no individual data were available on this [118,119]. There was insufficient patient data to consider regional variance in solar insolation that has occurred over decadal timeframes.

4.2. Conclusions

In patients with BD I, increasing change in solar insolation during the year, between winter and summer or tropical wet and dry seasons, was associated with a first episode with a polarity of depression. Physicians who practice in locations with a large change in solar insolation across the year should monitor even more carefully for BD. Increased awareness and research into the role of circadian dysfunction throughout the course of BD is needed.

Declaration of Competing Interest

Rasmus W. Licht has received research grants from Glaxo Smith Kline, honoraria for lecturing from Pfizer, Glaxo Smith Kline, Eli Lilly, Astra-Zeneca, Bristol-Myers Squibb, Janssen Cilag, Lundbeck, Otsuka, Servier and honoraria from advisory board activity from Glaxo Smith Kline, Eli Lilly, Astra-Zeneca, Bristol-Myers Squibb, Janssen Cilag, Sunovion and Sage. All other authors report no competing interests.

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