Relationship between sunlight and the age of onset of bipolar disorder: An international multisite study

Michael Bauer, Tasha Glenn, Martin Alda, Ole A. Andreassen, Elias Angelopoulos, Raffaella Ardau, Christopher Baethge, Rita Bauer, Frank Bellivier, Robert H. Belmaker, Michael Berk, Thomas D. Bjella, Letizia Bossini, Yuly Bersudsky, Eric Yat Wo Cheung, Jorn Conell, Maria Del Zompo, Seetal Dodd, Bruno Etain, Andrea Fagiolini, Mark A. Frye, Kostas N. Fountoulakis, Jade Garneau-Fournier, Ana Gonzalez-Pinto, Hirohiko Harima, Stefanie Hassel, Chantal Henry, Apostolos Iacovides, Erkki T. Isometsä, Flávio Kapczinski, Sebastian Kliwicki, Barbara König, Rikke Krogh, Mauricio Kunz, Beny Lafer, Erik R. Larsen, Ute Lewitzka, Carlos Lopez-Jaramillo, Glenda MacQueen, Mirko Manchia, Wendy Marsh, Mónica Martinez-Cengotitabengoa, Ingrid Melle, Scott Monteith, Gunnar Morken, Rodrigo Munoz, Fabiano G. Nery, Claire O'Donovan, Yamima Osher, Andrea Pfennig, Danilo Quiroz, Raj Ramesar, Natalie Rasgon, Andreas Reif, Philipp Ritter, Janusz K. Rybakowski, Kemal Sagduyu, Ângela M. Scippa, Emanuel Severus, Christian Simhandl, Dan Stein, Sergio Strejilevich, Ahmad Hatim Sulaiman, Kirsi Suominen, Hiromi Tagata, Yoshitaka Tatebayashi, Carla Torrent, Eduard Vieta, Biju Viswanath, Mihir J. Wanchoo, Mark Zetin, Peter C. Whybrow

PII: S0165-0327(14)00327-9
DOI: <http://dx.doi.org/10.1016/j.jad.2014.05.032>
Reference: JAD6777

To appear in: *Journal of Affective Disorders*

Received date: 28 February 2014

Revised date: 20 May 2014

Accepted date: 21 May 2014

Cite this article as: Michael Bauer, Tasha Glenn, Martin Alda, Ole A. Andreassen, Elias Angelopoulos, Raffaella Arda, Christopher Baethge, Rita Bauer, Frank Bellivier, Robert H. Belmaker, Michael Berk, Thomas D. Bjella, Letizia Bossini, Yuly Bersudsky, Eric Yat Wo Cheung, Jorn Conell, Maria Del Zompo, Seetal Dodd, Bruno Etain, Andrea Fagiolini, Mark A. Frye, Kostas N. Fountoulakis, Jade Garneau-Fournier, Ana Gonzalez-Pinto, Hirohiko Harima, Stefanie Hassel, Chantal Henry, Apostolos Iacovides, Erkki T. Isometsä, Flávio Kapczinski, Sebastian Kliwicki, Barbara Konig, Rikke Krogh, Mauricio Kunz, Beny Lafer, Erik R. Larsen, Ute Lewitzka, Carlos Lopez-Jaramillo, Glenda MacQueen, Mirko Manchia, Wendy Marsh, Mónica Martinez-Cengotitabengoa, Ingrid Melle, Scott Monteith, Gunnar Morken, Rodrigo Munoz, Fabiano G. Nery, Claire O'Donovan, Yamima Osher, Andrea Pfennig, Danilo Quiroz, Raj Ramesar, Natalie Rasgon, Andreas Reif, Philipp Ritter, Janusz K. Rybakowski, Kemal Sagduyu, Ângela M. Scippa, Emanuel Severus, Christian Simhandl, Dan Stein, Sergio Strejilevich, Ahmad Hatim Sulaiman, Kirsi Suominen, Hiromi Tagata, Yoshitaka Tatebayashi, Carla Torrent, Eduard Vieta, Biju Viswanath, Mihir J. Wanchoo, Mark Zetin, Peter C. Whybrow, Relationship between sunlight and the age of onset of bipolar disorder: An international multisite study, *Journal of Affective Disorders*, <http://dx.doi.org/10.1016/j.jad.2014.05.032>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting galley proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Relationship between sunlight and the age of onset of bipolar disorder: an international multisite study.

Corresponding author:

Michael Bauer, MD, PhD, Department of Psychiatry and Psychotherapy,

Universitätsklinikum Carl Gustav Carus, Technische Universität Dresden, Germany

Fetscherstr. 74, 01307 Dresden, Germany Phone: +49-351- 458-0, Fax: +49-30-450-

51 79 62 michael.bauer@uniklinikum-dresden.de

Michael Bauer¹, Tasha Glenn², Martin Alda³, Ole A. Andreassen⁴, Elias Angelopoulos⁵, Raffaella Ardu⁶, Christopher Baethge⁷, Rita Bauer¹, Frank Bellivier⁸, Robert H Belmaker⁹, Michael Berk^{10,11}, Thomas D Bjella⁴, Letizia Bossini¹², Yuly Bersudsky⁹, Eric Yat Wo Cheung¹³, Jörn Conell¹, Maria Del Zompo¹⁴, Seetal Dodd^{10,15}, Bruno Etain¹⁶, Andrea Fagiolini¹², Mark A. Frye¹⁷, Kostas N Fountoulakis¹⁸, Jade Garneau-Fournier¹⁹, Ana Gonzalez-Pinto²⁰, Hirohiko Harima²¹, Stefanie Hassel²², Chantal Henry¹⁶, Apostolos Iacovides¹⁸, Erkki T Isometsä^{23,24}, Flávio Kapczinski²⁵, Sebastian Kliwiczki²⁶, Barbara König²⁷, Rikke Krogh²⁸, Mauricio Kunz²⁵, Beny Lafer²⁹, Erik R Larsen²⁸, Ute Lewitzka¹, Carlos Lopez-Jaramillo³⁰, Glenda MacQueen²², Mirko Manchia³, Wendy Marsh³¹, Mónica Martinez-Cengotitabengoa²⁰, Ingrid Melle⁴, Scott Monteith³², Gunnar Morken³³, Rodrigo Munoz³⁴, Fabiano G Nery²⁹, Claire O'Donovan³, Yamima Osher⁹, Andrea Pfennig¹, Danilo Quiroz³⁵, Raj Ramesar³⁶, Natalie Rasgon¹⁹, Andreas Reif³⁷, Philipp Ritter¹, Janusz K Rybakowski²⁶, Kemal Sagduyu³⁸, Ângela M Scippa³⁹, Emanuel Severus¹, Christian Simhandl²⁷, Dan Stein⁴⁰, Sergio Strejilevich⁴¹, Ahmad Hatim Sulaiman⁴², Kirsi Suominen⁴³, Hiromi Tagata²¹, Yoshitaka Tatebayashi⁴⁴, Carla Torrent⁴⁵, Eduard Vieta⁴⁵, Bijou Viswanath⁴⁶, Mihir J Wanchoo¹⁷, Mark Zetin⁴⁷, Peter C Whybrow⁴⁸

¹Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Technische Universität Dresden, Germany

²ChronoRecord Association, Fullerton, CA, USA

³Department of Psychiatry, Dalhousie University, Halifax, NS Canada

⁴NORMENT - K.G. Jebsen Centre for Psychosis Research, Division of Mental Health and Addiction, Oslo University Hospital & Institute of Clinical Medicine, Oslo, Norway

⁵Department of Psychiatry, University of Athens Medical School, Eginition Hospital, Athens, Greece

⁶Unit of Clinical Pharmacology, University-Hospital of Cagliari, Italy

⁷Department of Psychiatry and Psychotherapy, University of Cologne Medical School, Cologne, Germany

⁸Psychiatrie, GH Saint-Louis – Lariboisière – F. Widal, APHP, INSERM UMR-S1144, Faculté de Médecine, Université D. Diderot, Paris and FondaMental Fondation, Créteil, France

⁹Department of Psychiatry, Faculty of Health Sciences, Ben Gurion University of the Negev; Beer Sheva Mental Health Center, Beer Sheva Israel

¹⁰ IMPACT Strategic Research Centre, School of Medicine, Deakin University, Geelong, Victoria 3220, Australia

¹¹Department of Psychiatry, ORYGEN Youth Health Research Centre, Centre for Youth Mental Health and the Florey Institute for Neuroscience and Mental Health, University of Melbourne, Parkville, Victoria 3052, Australia.

¹²Department of Molecular Medicine and Department of Mental Health (DAI) University of Siena and University of Siena Medical Center (AOUS), Siena, Italy

¹³Department of General Adult Psychiatry, Castle Peak Hospital, Hong Kong

¹⁴Section of Neurosciences and Clinical Pharmacology, Department of Biomedical Sciences, University of Cagliari, Sardinia, Italy

¹⁵Department of Psychiatry, University of Melbourne, Parkville, Victoria 3052, Australia

¹⁶AP-HP, Hopitaux Universitaires Henri Mondor and INSERM U955 (IMRB) and Université Paris Est and Fondation Fondamental, Creteil, France

¹⁷Department of Psychiatry, & Psychology, Mayo Clinic Depression Center, Mayo Clinic, Rochester, MN, USA

¹⁸3rd Department of Psychiatry, Division of Neurosciences, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece

¹⁹Department of Psychiatry and Behavioral Sciences, Stanford School of Medicine, Palo Alto, CA, USA

²⁰Department of Psychiatry, University Hospital of Alava, University of the Basque Country, CIBERSAM, Vitoria, Spain

²¹Department of Psychiatry, Tokyo Metropolitan Matsuzawa Hospital, Setagaya, Tokyo, Japan

²²Department of Psychiatry, Faculty of Medicine, University of Calgary, Calgary, AB, Canada

²³Department of Psychiatry, Institute of Clinical Medicine, University of Helsinki, Finland

²⁴National Institute for Health and Welfare, Helsinki, Finland

²⁵Laboratory of Molecular Psychiatry, Hospital de Clínicas de Porto Alegre, Federal University of Rio Grande do Sul, Porto Alegre, Brazil

²⁶Department of Adult Psychiatry, Poznan University of Medical Sciences, Poznan, Poland

²⁷BIPOLAR Zentrum Wiener Neustadt, Wiener Neustadt, Austria

²⁸Dept. of Affective Disorders, Q, Mood Disorders Research Unit, Aarhus University Hospital, Denmark

²⁹Bipolar Disorder Research Program, Department of Psychiatry, University of São Paulo Medical School, São Paulo, Brazil

³⁰Mood Disorders Program, Fundacion San Vicente de Paul, Department of Psychiatry, Universidad de Antioquia, Medellín, Colombia

³¹Department of Psychiatry, University of Massachusetts, Worcester, MA, USA

³²Michigan State University College of Human Medicine, Traverse City Campus, Traverse City, MI, USA

³³Department of Neuroscience, NTNU, and St Olavs' University Hospital, Trondheim, Norway

³⁴Department of Psychiatry, University of California San Diego, San Diego, CA USA

³⁵Department of Psychiatry, Diego Portales University, Santiago, Chile

³⁶UCT/MRC Human Genetics Research Unit, Division of Human Genetics, Institute of Infectious Disease and Molecular Medicine, , University of Cape Town, Anzio Road, Observatory, 7925, South Africa

³⁷Department of Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Würzburg, Germany

³⁸Department of Psychiatry, University of Missouri Kansas City School of Medicine, Kansas City, MO, USA

³⁹Department of Neuroscience and Mental Health, Federal University of Bahia, Salvador, Brazil

⁴⁰Department of Psychiatry, University of Cape Town, Cape Town, South Africa

⁴¹Bipolar Disorder Program, Neuroscience Institute, Favaloro University, Buenos Aires, Argentina

⁴²Department of Psychological Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

⁴³City of Helsinki, Department of Social Services and Health Care, Psychiatry, Helsinki, Finland

⁴⁴Schizophrenia & Affective Disorders Research Project, Tokyo Metropolitan Institute of Medical Science, Seatagaya, Tokyo, Japan

⁴⁵Clinical Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia, Spain

⁴⁶Department of Psychiatry, NIMHANS, Bangalore-560029, India

⁴⁷Department of Psychology, Chapman University, Orange, CA, USA

⁴⁸Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior University of California Los Angeles (UCLA), Los Angeles, CA, USA

Abstract:

Background: The onset of bipolar disorder is influenced by the interaction of genetic and environmental factors. We previously found that a large increase in sunlight in springtime was associated with a lower age of onset. This study extends this analysis with more collection sites at diverse locations, and includes family history and polarity of first episode.

Methods: Data from 4037 patients with bipolar I disorder were collected at 36 collection sites in 23 countries at latitudes spanning 3.2 north (N) to 63.4 N and 38.2 south (S) of the equator. The age of onset of the first episode, onset location, family history of mood disorders, and polarity of first episode were obtained retrospectively, from patient records and/or direct interview. Solar insolation data were obtained for the onset locations.

Results: There was a large, significant inverse relationship between maximum monthly increase in solar insolation and age of onset, controlling for the country median age and the birth cohort. The effect was reduced by half if there was no family history. The maximum monthly increase in solar insolation occurred in springtime. The effect was one-third smaller for initial episodes of mania than depression. The largest maximum monthly increase in solar insolation occurred in northern latitudes such as Oslo, Norway, and warm and dry areas such as Los Angeles, California.

Limitations: Recall bias for onset and family history data

Conclusions: A large springtime increase in sunlight may have an important influence on the onset of bipolar disorder, especially in those with a family history of mood disorders.

Key words: bipolar disorder, age of onset, sunlight, insolation

Accepted manuscript

1. Introduction

Sunlight provides warmth, stimulates vision, initiates vitamin D synthesis, and plays a fundamental role in how the circadian clock adapts human physiology and behavior to the alternation of day and night (Berson 2003; Brainard and Hanifin, 2005; Hatori and Panda, 2010). Circadian rhythms are involved in regulation of mood (Albrecht 2010; McClung 2013) and abnormalities in circadian rhythms are thought to underlie bipolar disorder (Goodwin and Jamison, 1990; Mansour et al., 2005; McClung 2007). We previously found that the larger the springtime increase in solar electromagnetic energy striking the surface of the earth (insolation) at the onset location, the younger the age of onset of bipolar disorder (Bauer et al., 2012).

The emergence of bipolar disorder involves the interaction of complex genetic mechanisms (Burmeister et al., 2008; Craddock and Sklar, 2013; Petronis 2003) and environmental factors (Tsuchiya et al., 2003). Based on 6 studies of 2509 patients with bipolar I disorder, the weighted mean age of onset falls into 3 groups, having peaks at ages 18.1, 26.9 and 42.7 years, with 55% of patients in the middle or late onset groups (Bellivier et al., 2001; Bellivier et al., 2003; González Pinto et al., 2009; Hamshere et al., 2009; Lin et al., 2006; Manchia et al., 2008). This broad range of onset and the polygenic basis of bipolar disorder suggest that environmental factors have an influential role (Burmeister et al., 2008; Craddock and Sklar, 2013; Wright et al., 2003). Environmental factors associated with a younger age of onset are cannabis use (González-Pinto et al., 2008; Lagerberg et al., 2011), stressful life events (Hoersh et al., 2011) and childhood abuse (Garno et al., 2005; Leverich et al., 2002), while

neurological illness is associated with an older onset (Depp and Jeste, 2004). The purpose of this study was to repeat our prior investigation of the association between solar insolation and the age of onset of bipolar disorder using a substantially larger sample, and including information on family history and polarity of the first episode.

2. Methods

2.1 Patient data

All patients included in this study had a diagnosis of bipolar disorder according to DSM-IV criteria made by a psychiatrist. Approval for this study was obtained from institutional review boards according to local requirements. Patient data were obtained retrospectively at 36 collection sites in 23 countries. In 20 sites (Athens, Greece; Bangalore, India; Buenos Aires, Argentina; Cagliari, Sardinia, Italy; Dresden, Germany; Halifax, Canada; Helsinki, Finland; Hong Kong; Kansas City, KS, USA; Los Angeles, CA, USA; Medellín, Colombia; Oslo, Norway; Paris, France; Porto Alegre, Brazil; Rochester, MN, USA; San Diego, CA, USA; Santiago, Chile; Siena, Italy; Thessaloniki, Greece; Würzburg, Germany), data were gathered by direct interviews and reviewing records, in 8 sites (Barcelona, Spain; Melbourne/Geelong, Australia; Palo Alto, CA, USA; São Paulo, Brazil; Salvador, Brazil; Trondheim, Norway; Vitoria-Basque Country, Spain; Worcester, MA, USA) primarily by direct interviews, and at the remaining 8 sites (Aarhus, Denmark; Beer Sheva, Israel; Calgary, Canada; Cape Town, South Africa; Kuala Lumpur, Malaysia; Poznan, Poland; Tokyo, Japan; Wiener Neustadt, Austria) primarily by reviewing records.

Variables included sex, date of birth, age of onset, location of onset, family history of any mood disorder in a first degree relative, and polarity of the first episode (depressed, manic or hypomanic). The age of onset was defined as the first occurrence of an episode of depression, mania or hypomania according to DSM-IV criteria.

2.2 Potential confounders

Apart from any solar insolation effects, there were two potential age-related confounders. The country median age varied by about 20 years between the oldest (Japan 45.8 years) and youngest (South Africa at 25.5) collection sites. For a disease with a variable age of onset that spans several decades, an older age of onset would be expected in a country with an older population (Chen et al., 1993; Heimbuch et al., 1980). The country median age was included in all models to reflect the differences in country population.

Previous research reported a large birth cohort effect in bipolar disorder with an older onset in older cohorts (Chengappa et al., 2003), and that less than 10% of people develop bipolar disorder after age 50 (Vasudev and Thomas, 2010). Since the current data includes a large percentage of people born before 1960 (36.8%), three birth cohort groups were created: born before 1940, born between 1940 and 1959, and born after 1959 (Chengappa et al., 2003). The birth cohort grouping variable was included in all models.

There was a large imbalance in the percent of patients with a diagnosis of bipolar I disorder as compared to other bipolar subtypes. Since the percent of bipolar I varied from 23% to 99%, with 40% of collection sites having $\geq 80\%$ of patients with bipolar I disorder, only patients with a diagnosis of bipolar I disorder were included in the analysis.

2.3 Solar Insolation data

All solar insolation data were obtained from the US National Aeronautics and Space Administration (NASA) Surface Meteorology and Solar Energy (SSE) Version 6.0 database, which is based on data collected over a 22 year time period from 1983-2005 (NASA 2012). Average monthly solar insolation data are available for the entire globe with a spatial resolution of 1 x 1 degree latitude/longitude. Solar insolation is a measure of the electromagnetic energy from the sun received for a given surface area on earth at a given time, expressed in kWh/m²/day (kilowatt hours/square meter/day). Solar insolation is not evenly distributed across the earth's surface. The solar insolation varies with the annual changes to the earth-sun relationship (angle of incidence which the sun's rays strike the earth, the day length, and the latitude), reflection, scattering and absorption of the sun's rays by clouds and aerosols in the atmosphere, and reflection back into space by snow, ice, and desert sand on the earth's surface (NASA 2010).

The overall pattern of monthly changes to solar insolation varies greatly by latitude. At the equator, there is very little change to solar insolation throughout the year.

Generally, the closer to the poles, the greater the range in solar insolation across the

year. See Figure 1 for examples of monthly changes in insolation at collection sites in this study. Additionally, locations at the same latitude may have very different solar insolation due to local conditions such as cloud cover, altitude, and proximity to large bodies of water. **For example, Rome, Italy and Chicago IL, US have the same latitude of 41.9 degrees north (N) and the same hours of daylight. However the maximum monthly increase in solar insolation is 1.4 kWh/m²/day in Rome but only 1.01 kWh/m²/day in Chicago, occurring between February and March for both cities.**

2.4 Solar insolation variables

Onset location data from every patient were grouped into reference cities. Each reference city represents all locations within the 1 x 1 degree grid of latitude and longitude. For example, Dresden with latitude of 51.1 N and 13.8 degrees east (E) is the reference city for all onset locations between 51 and 52 degrees N, and 13 and 14 degrees E. The monthly solar insolation data for reference cities in the southern hemisphere were shifted by 6 months to be comparable with monthly solar insolation in the northern hemisphere. The number of reference cities from each collection site varied considerably reflecting country size, migration patterns and cultural differences.

Monthly, yearly and seasonal variables were created using the solar insolation data for each reference city including the monthly increase and decrease in solar insolation, the yearly cumulative solar insolation, and the yearly minimum and maximum monthly solar insolation. The interaction between maximum monthly increase in solar insolation x

family history, and maximum monthly increase in solar insolation x polarity of first episode were also analyzed.

2.5 Country specific variables

The variables available for each country for each reference city included the lifetime prevalence of bipolar I disorder, the country median age, and the country sex ratio for ages 15-64 (CIA World Factbook).

2.6 Statistics

Generalized estimating equations (GEE) models were used to estimate the effect of solar insolation on the age of onset. The GEE method corrects for the correlated data within each reference city (cluster) (Zeger and Liang, 1986), estimates the difference in magnitude of the association between two variables through the use of interaction terms, and estimates the effect across the entire population rather than within a cluster. All GEE models used age of onset as the dependent variable. An exchangeable correlation matrix was chosen, as appropriate for a large number of clusters with variable cluster sizes including many with a single observation (Stedman et al., 2008; Zeger and Liang, 1986). To further evaluate the birth cohort effect, models were also estimated that excluded both patients born before 1960 and the birth cohort variable. The model fit was assessed using the quasi-likelihood independent model criterion that is suitable for GEE (Pan 2001). A significance level of 0.01 was used to evaluate estimated coefficients. Sidak's adjustment was used to evaluate multiple comparisons at the 0.01 level. SPSS Version 22 was used for all analyses.

3. Results

Data were collected for a total of 5465 patients. Of the 5465 patients, 4037 had a diagnosis of bipolar I disorder, 1236 had bipolar II and 192 had bipolar NOS. Only the 4037 patients with a diagnosis of bipolar I disorder were included in the analysis. The 4037 patients included 2414 from the prior analysis (Bauer et al., 2012). Of the 4037 patients, 2374 (58.8%) were female and 1663 (41.2%) were male. Family history was available for 3334 (82.6%) of the 4037 patients and polarity of first episode was available for 3600 (89.2%).

The mean age of the patients was 48.1 ± 14.5 years. For comparison with prior international studies, the unadjusted age of onset for the 4037 patients was 25.4 ± 10.7 years, similar to previous reports of 25.7 years, $n=1665$ (Baldessarini et al., 2012) and 25.6 years, $n=1041$ (Morselli et al., 2003). Of the 4037 patients, 220 (5.4%) were born before 1940, 1267 (31.4%) were born between 1940 and 1959, and 2550 (63.2%) were born after 1959. As expected, country median age and birth cohort were significantly associated with the age of onset (both $p<0.001$).

Although data for the 4037 patients were collected at 36 collection sites in 23 countries, the onset locations were in 318 unique reference cities or clusters in 43 countries. The onset location was in northern hemisphere for 2994 patients and in the southern hemisphere for 1043 patients. The distribution of the onset locations across latitudes is

shown in Table 1. The mean number of patients in each reference city was 12.7 with 4.3% of the 4037 patients in a reference city of one.

The best fitting model included the interaction of the maximum monthly increase in solar insolation x family history, the country median age and the birth cohort. This is labeled Model 1. The primary result was an inverse relationship between maximum monthly increase in solar insolation and age of onset, which was reduced by about 50% if there was no family history. **To put these results in perspective, when comparing 2 regions with a difference of 0.1 kWh/m²/day in the maximum monthly increase in solar insolation, the region with the larger increase is associated with a 0.4862 year or nearly 6 months younger age of onset when there is a family history of bipolar disorder, as compared to the region with the smaller increase. If there is no family history, this difference is reduced to 0.2552 year or about 3 months.**

There were similar results when Model 1 was run excluding patients born before 1960 and the birth cohort. Model 2 included the interaction of the maximum monthly increase in solar insolation x polarity of first episode, the country median age and the birth cohort, and was also significant. The results also showed the inverse relationship between maximum monthly increase in solar insolation and age of onset, but the effect was about 1/3 smaller for initial episodes of mania. Similar results for Model 2 were also obtained when excluding patients born before 1960 and the birth cohort. See Tables 2 and 3.

The maximum monthly increase in solar insolation occurred in springtime: between February and March in 40% of onset locations, between March and April in 38% of onset locations, and between April and May in 11% of onset locations, excluding the locations near the equator that have little monthly change in solar insolation throughout the year. The maximum increase in solar insolation occurred in diverse latitudes.

Table 4 shows the mean age of onset adjusted for country median age and birth cohort by the maximum monthly increase in solar insolation.

The collection site was thought to adequately serve as a proxy for the specific onset location for patients from Barcelona, Cape Town, Helsinki, Melbourne/Geelong, Porto Alegre, São Paulo, Salvador, Vitoria, and Würzburg. The best fitting model was run excluding all these sites and the magnitude of the estimated coefficients did not change substantially and remained significant at the 0.01 level.

The age of onset was also associated with range of monthly solar insolation but the model was not as good a fit as with the maximum monthly increase. As in our prior study, the yearly cumulative solar insolation, the maximum decrease in monthly solar insolation, the yearly minimum and maximum monthly solar insolation, latitude, sex, country prevalence of bipolar I disorder, and country sex ratio were not significantly associated with the age of onset.

4. Discussion

The maximum monthly increase in solar insolation in springtime was inversely associated with the age of onset of bipolar disorder, but this effect was reduced by half in those without a family history of mood disorders. This finding replicated the results of our initial study (Bauer et al., 2012) with a sample that is 67% larger in size and contains 77% more reference cities. The interaction with family history suggests there may be a genetic predisposition to some physiological responses to sunlight, and highlights the importance of obtaining a family history from all patients. This finding is also consistent with many prior reports that family history is associated with a younger age of onset (Baldessarini et al., 2012; Lin et al., 2006; Post et al., 2013; Schürhoff et al., 2000).

Both the collection sites and the onset locations were distributed across all latitudes in both hemispheres, and represent a wide range of solar insolation profiles including arid, sub-arctic, equatorial as well as temperate. In locations that experience a large increase in sunlight in springtime, detailed questioning to detect symptoms of bipolar disorder, and closer monitoring of patients and their adolescent children may be indicated. Conversely, in locations with little change in sunlight throughout the year, the onset of bipolar disorder may be at an older age than expected from studies conducted in temperate climates. The effect of the maximum monthly increase in solar insolation on the age of onset is one-third smaller for those with a first episode of mania rather than depression, in line with prior observation that a first episode of depression occurs at a younger age than mania (Forty et al., 2009; Ortiz et al., 2011; Perlis et al., 2005).

Both longstanding clinical observation of circadian dysfunction in bipolar disorder, and active ongoing research into circadian genes and phenotypes support the concept that a large monthly increase in solar insolation may be associated with disease onset (Goodwin and Jamison 1990; Mansour et al., 2005; McCarthy et al., 2012; McClung 2007; Whybrow 1997). The recent progress in understanding how light changes are unconsciously captured and transmitted to the circadian system (Benarroch 2011; Foster and Hankins, 2007; Hatori and Panda, 2010) may someday help to explain the solar insolation findings in this study. Photosensitive retinal ganglion cells (pRGC) containing the pigment melanopsin mediate a broad range of non-image forming functions including circadian synchronization, melatonin suppression and alertness (Berson 2003, Gooley et al., 2003; Zaidi et al., 2007). The intrinsic photosensitivity of pRGC is specialized to detect fluctuations in intensity of environmental light (Berson 2003, Hatori and Panda, 2010) and the signals are sent to the circadian pacemaker in the suprachiasmatic nucleus (SCN). The peak spectral absorption for non-image forming functions is at short wavelength of visible light, or blue light: ~480 nm for melanopsin (Berson et al., 2002), ~460 nm for melatonin suppression (Brainard et al., 2001), and ~470 nm for alertness (Stephenson et al., 2012). Similarly, the dominant wavelength of morning sunlight was measured at 477 nm in the US (Gallagher III et al., 1996; Turner and Mainster, 2008).

Although people who live at latitudes with a short daylength have less exposure to solar insolation during winter, indoor lighting is optimized for vision (Andersen et al., 2012;

van Bommel 2006; van Bommel and van den Beld, 2004). In contrast to circadian photoreception, peak absorptions for vision are at longer wavelength: rod-mediated dim light vision at 506 nm or green light, and cone-mediated bright/moderate light vision at 555 nm or green-yellow light (Turner and Mainster, 2008). Standard lighting, such as incandescent, fluorescent warm, and low pressure sodium lamps, has a dominant wavelength of about 575 nm (Bellia et al., 2011) and less than 5% of the intensity of sunlight. However, unlike with vision, insufficient circadian light exposure is not perceived (Turner et al., 2010). There are ongoing efforts to develop new standards for indoor lighting that address circadian as well as visual effects, and will consider the spectrum, intensity, timing of exposure, duration of signal, and ocular physiology (Andersen et al., 2012; Bellia et al., 2011; van Bommel and van den Beld, 2004).

While blue light may be the most important component of solar insolation from a circadian perspective, its role in the emergence of bipolar disorder is not known. The spectral composition of sunlight varies with the time of day, season and latitude (Thorne et al., 2009) and younger people may be particularly sensitive to a springtime increase in blue light. Young eyes only need about half the circadian illuminance as middle aged eyes due to age-related decreases in pupil area and crystalline lens transmission (Turner et al., 2010). In animal studies, abnormal light cycles increased depression-like behavior and impaired learning in normal mice, but not in mice without pRGC (LeGates et al., 2012). Blue light exposure also stimulates cognitive brain activity in normal and blind individuals as detected by fMRI (Stephenson et al., 2012; Vandewalle et al., 2007; Vandewalle et al., 2013). Preliminary studies of patients with seasonal affective

disorder (SAD) found blue light treatment to be more effective than red light (Anderson et al., 2009; Glickman et al., 2006), and that sequence variation in the melanopsin gene may increase vulnerability to SAD (Rocklein et al., 2009).

Other recent evidence supports the importance of a large monthly increase in solar insolation. In patients with depression, there were more early responders to paroxetine when sunlight was increasing during springtime (Tomita et al., 2012). Seasonal variation with an increase in the spring-summer months was reported in the serum concentration of brain-derived-neurotrophic factor (BDNF) (Molendijk et al., 2012) and in serotonin turnover in cerebrospinal fluid (Luykx et al., 2013), and these may be involved in the pathophysiology of depression. Dose dependent suppression of melatonin by light (West et al., 2011) may be exaggerated in bipolar I disorder (Hallam et al., 2009). Vitamin D synthesis in skin requires sunlight exposure. Low vitamin D concentrations were associated with diverse psychiatric disorders (Berk et al., 2008), and by meta-analysis, with depression (Anglin et al., 2013; Annweiler et al., 2013) and poor cognition (Balion et al., 2012). Finally, some patients with depression show anomalies in the retinal response to light (Fountoulakis 2010; Fountoulakis et al., 2005).

4.1 Limitations

There are several limitations to this study. The diagnosis of bipolar disorder was based on the DSM-IV criteria, but the processes of diagnostic assessment and data gathering were not standardized across the collection sites. Self-reported age of onset data are subject to recall bias, however this approach was used in related research (Baldessarini

et al., 2012; Forty et al., 2009; Lin et al., 2006; Perlis et al., 2005). Family history data is often inaccurate and more reliable for severe disorders (Hardt and Franke, 2007), and may be influenced by cultural attitudes towards mental illness (Karasz 2005). Individual exposure to sunlight such as for outdoor workers was not assessed, although most people in industrialized countries work indoors and have indoor hobbies (Godar 2005; Pergams and Zaradic, 2008). This study did not include other environmental factors that may affect the age of onset such as drug abuse, or factors known to disrupt circadian rhythms such as night shift work or irregular lifestyles (Kapczinski et al., 2011; Rosa et al., 2013). Shifting data from the southern hemisphere by six months ignores local cultural dimensions of seasonality.

4.2 Conclusions

In conclusion, the monthly increase in solar insolation may have a significant impact on the age of onset of bipolar disorder, especially in those with a family history of mood disorders. The larger the maximum monthly increase in solar insolation in springtime, the younger the onset of bipolar disorder. A first episode of depression occurred at a younger age than mania, despite the effects of a large springtime increase in solar insolation. Research into the effects of the duration, intensity, timing and wavelength of light is needed in bipolar disorder.

Acknowledgements

We would like to thank the International Society of Bipolar Disorders for supporting this project.

References:

- Albrecht, U., 2010. Circadian clocks in mood-related behaviors. *Ann. Med.* 42, 241-251.
- Andersen, M., Mardaljevic, J., Lockley, S.W., 2012. A framework for predicting the non-visual effects of daylight – Part I: photobiology- based model. *Light. Res. Technol.* 44, 37-53.
- Anderson, J.L., Glod, C.A., Dai, J., Cao, Y., Lockley, S.W., 2009. Lux vs. wavelength in light treatment of Seasonal Affective Disorder. *Acta Psychiatr. Scand.* 120, 203-212.
- Anglin, R.E., Samaan, Z., Walter, S.D., McDonald, S.D., 2013. Vitamin D deficiency and depression in adults: systematic review and meta-analysis. *Br. J. Psychiatry.* 202, 100-107.
- Annweiler, C., Rastmanesh, R., Richard-Devantoy, S., Beauchet, O., 2013. The role of vitamin D in depression: from a curious idea to a therapeutic option. *J. Clin. Psychiatry.* 74, 1121-1122.
- Baldessarini, R.J., Tondo, L., Vazquez, G.H., Undurraga, J., Bolzani, L., Yildiz, A., Khalsa, H.M., Lai, M., Lepri, B., Lolich, M., Maffei, P.M., Salvatore, P., Faedda, G.L., Vieta, E., Tohen, M., 2012. Age at onset versus family history and clinical outcomes in 1,665 international bipolar-I disorder patients. *World Psychiatry.* 11, 40-46.

- Balton, C., Griffith, L.E., Striffler, L., Henderson, M., Patterson, C., Heckman, G., Llewellyn, D.J., Raina, P., 2012. Vitamin D, cognition, and dementia: a systematic review and meta-analysis. *Neurology*. 79, 1397-1405.
- Bauer, M., Glenn, T., Alda, M., Andreassen, O.A., Arda, R., Bellivier, F., Berk, M., Bjella, T.D., Bossini, L., Del Zompo, M., Dodd, S., Fagiolini, A., Frye, M.A., Gonzalez-Pinto, A., Henry, C., Kapczinski, F., Kliwicky, S., König, B., Kunz, M., Lafer, B., Lopez-Jaramillo, C., Manchia, M., Marsh, W., Martinez-Cengotitabengoa, M., Melle, I., Morken, G., Munoz, R., Nery, F.G., O'Donovan, C., Pfennig, A., Quiroz, D., Rasgon, N., Reif, A., Rybakowski, J., Sagduyu, K., Simhandl, C., Torrent, C., Vieta, E., Zetin, M., Whybrow, P.C., 2012. Impact of sunlight on the age of onset of bipolar disorder. *Bipolar Disord*. 14, 654-663.
- Bellia, L., Bisegna, F., Spada, G., 2011. Lighting in indoor environments: Visual and non-visual effects of light sources with different spectral power distributions. *Build Environ*. 46, 1984-1992.
- Bellivier, F., Golmard, J.L., Henry, C., Leboyer, M., Schürhoff, F., 2001. Admixture analysis of age at onset in bipolar I affective disorder. *Arch. Gen. Psychiatry*. 58, 510-512.
- Bellivier F., Golmard J.L., Rietschel M., Schulze T.G., Malafosse A., Preisig M., McKeon P., Mynett-Johnson L., Henry C., Leboyer M., 2003. Age at onset in bipolar I affective disorder: further evidence for three subgroups. *Am. J. Psychiatry*. 160, 999-1001.
- Benarroch, E.E., 2011. The melanopsin system: Phototransduction, projections, functions, and clinical implications. *Neurology*. 76, 1422-1427.

- Berk, M., Jacka, F.N., Williams, L.J., Ng, F., Dodd, S., Pasco, J.A., 2008. Is this D vitamin to worry about? Vitamin D insufficiency in an inpatient sample. *Aust. N. Z. J. Psychiatry.* 42, 874-878.
- Berson, D.M., 2003. Strange vision: ganglion cells as circadian photoreceptors. *Trends Neurosci.* 26, 314-320.
- Berson, D.M., Dunn, F.A., Takao, M., 2002. Phototransduction by retinal ganglion cells that set the circadian clock. *Science.* 295, 1070-1073.
- Brainard, G.C., Hanifin, J.P., 2005. Photons, clocks, and consciousness. *J. Biol. Rhythms.* 20, 314-325.
- Brainard, G.C., Hanifin, J.P., Greeson, J.M., Byrne, B., Glickman, G., Gerner, E., Rollag M.D., 2001. Action spectrum for melatonin regulation in humans: evidence for a novel circadian photoreceptor. *J. Neurosci.* 21, 6405-6412.
- Burmeister, M., McInnis, M.G., Zöllner, S., 2008. Psychiatric genetics: progress amid controversy. *Nat. Rev. Genet.* 9, 527-540.
- Chen, W.J., Faraone, S.V., Orav, E.J., Tsuang, M.T., 1993. Estimating age at onset distributions: the bias from prevalent cases and its impact on risk estimation. *Genet. Epidemiol.* 10, 43-59.
- Chengappa, K.N., Kupfer, D.J., Frank, E., Houck, P.R., Grochocinski, V.J., Cluss, P.A., Stapf, D.A., 2003. Relationship of birth cohort and early age at onset of illness in a bipolar disorder case registry. *Am. J. Psychiatry.* 160, 1636-1642.
- CIA World Factbook (<https://www.cia.gov/library/publications/the-world-factbook/>)
Accessed Jan 20, 2014.

- Craddock, N., Sklar, P., 2013. Genetics of bipolar disorder. *Lancet*. 381, 1654-1662.
- Depp, C.A., Jeste, D.V., 2004. Bipolar disorder in older adults: a critical review. *Bipolar Disord.* 6, 343-367.
- Forty, L., Jones, L., Jones, I., Smith, D.J., Caesar, S., Fraser, C., Gordon-Smith, K., Hyde, S., Craddock, N., 2009. Polarity at illness onset in bipolar I disorder and clinical course of illness. *Bipolar Disord.* 11, 82-88.
- Foster, R.G., Hankins, M.W., 2007. Circadian vision. *Curr. Biol.* 17, R746-751.
- Fountoulakis, K.N., 2010. Retinal response anomalies in patients with mental illness and high risk relatives. *Biol. Psychiatry.* 68, e3.
- Fountoulakis, K.N., Fotiou, F., Iacovides, A., Kaprinis, G., 2005. Is there a dysfunction in the visual system of depressed patients? *Ann. Gen. Psychiatry.* 29, 7.
- Gallagher III, F.W., Beasley, W.H., Bohren, C.F., 1996. Green thunderstorms observed. *Bulletin of the American Meteorological Society.* 77, 2889-2897.
- Garno, J.L., Goldberg, J.F., Ramirez, P.M., Ritzler, B.A., 2005. Impact of childhood abuse on the clinical course of bipolar disorder. *Br. J. Psychiatry.* 186, 121-125.
- Glickman, G., Byrne, B., Pineda, C., Hauck, W.W., Brainard, G.C., 2006. Light therapy for seasonal affective disorder with blue narrow-band light-emitting diodes (LEDs). *Biol. Psychiatry.* 59, 502-507.
- Godar, D.E., 2005. UV doses worldwide. *Photochem. Photobiol. Sci.* 81, 736-749.
- González Pinto, A., Barbeito, S., José Díaz, F., Vega, P., Mosquera, F., López, P., Alberich, S., Ruiz de Azua, S., Ugarte, A., Martín, M., de León, J., 2009. Age at

onset in bipolar I disorder: two may be better than three subgroups. *Rev. Psiquiatr. Salud. Ment.* 2, 29-34.

- González-Pinto A, Vega P, Ibáñez B, Mosquera F, Barbeito S, Gutiérrez M, Ruiz de Azúa S, Ruiz I, Vieta E., 2008. Impact of cannabis and other drugs on age at onset of psychosis. *J. Clin. Psychiatry.* 69, 1210-1216.
- Goodwin, F.K., Jamison, K.R., 1990. Sleep and biological rhythms. In: *Manic-Depressive Illness.* Oxford University Press:New York, NY, pp 541–574.
- Gooley, J.J., Lu, J., Fischer, D., Saper, C.B., 2003. A broad role for melanopsin in nonvisual photoreception. *J. Neurosci.* 23, 7093-7106.
- Hallam, K.T., Begg, D.P., Olver, J.S., Norman, T.R., 2009. Abnormal dose-response melatonin suppression by light in bipolar type I patients compared with healthy adult subjects. *Acta Neuropsychiatr.* 21, 246–255.
- Hamshire, M.L., Gordon-Smith, K., Forty, L., Jones, L., Caesar, S., Fraser, C., Hyde, S., Tredget, J., Kirov, G., Jones, I., Craddock, N., Smith, D.J., 2009. Age-at-onset in bipolar-I disorder: mixture analysis of 1369 cases identifies three distinct clinical sub-groups. *J. Affect. Disord.* 116, 23-29.
- Hardt, J., Franke, P., 2007. Validity, reliability and objectivity of the family history method in psychiatry: a meta analysis. *Eur. Psychiatry.* 22, 49-58.
- Hatori, M., Panda, S., 2010. The emerging roles of melanopsin in behavioral adaptation to light. *Trends Mol. Med.* 16, 435-446.
- Heimbuch, R.C., Matthysse, S., Kidd, K.K., 1980. Estimating age-of-onset distributions for disorders with variable onset. *Am. J. Hum. Genet.* 32, 564-574.

- Horesh, N., Apter, A., Zalsman, G., 2011. Timing, quantity and quality of stressful life events in childhood and preceding the first episode of bipolar disorder. *J. Affect. Disord.* 134, 434-437.
- Kapczinski, F., Frey, B.N., Vieta, E., 2011. Sleep and circadian rhythm disturbances in bipolar disorder: an urgent need for objective assessment and systematic follow-up. *J. Clin. Psychiatry.* 72, 724.
- Karasz, A., 2005. Cultural differences in conceptual models of depression. *Soc. Sci. Med.* 60, 1625-1635.
- Lagerberg, T.V., Sundet, K., Aminoff, S.R., Berg, A.O., Ringen, P.A., Andreassen, O.A., Melle, I., 2011. Excessive cannabis use is associated with earlier age at onset in bipolar disorder. *Eur. Arch. Psychiatry Clin. Neurosci.* 261, 397-405.
- LeGates, T.A., Altimus, C.M., Wang, H., Lee, H.K., Yang, S., Zhao, H., Kirkwood, A., Weber, E.T., Hattar, S., 2012. Aberrant light directly impairs mood and learning through melanopsin-expressing neurons. *Nature.* 491, 594-598.
- Leverich, G.S., McElroy, S.L., Suppes, T., Keck, P.E. Jr., Denicoff, K.D., Nolen, W.A., Altshuler, L.L., Rush, A.J., Kupka, R., Frye, M.A., Autio, K.A., Post, R.M., 2002. Early physical and sexual abuse associated with an adverse course of bipolar illness. *Biol. Psychiatry.* 51, 288-297.
- Lin, P.I., McInnis, M.G., Potash, J.B., Willour, V., MacKinnon, D.F., DePaulo, J.R., Zandi, P.P., 2006. Clinical correlates and familial aggregation of age at onset in bipolar disorder. *Am. J. Psychiatry.* 163, 240-246.

- Luykx, J.J., Bakker, S.C., van Geloven, N., Eijkemans, M.J., Horvath, S., Lentjes, E., Boks, M.P., Strengman, E., DeYoung, J., Buizer-Voskamp, J.E., Cantor, R.M., Lu, A., van Dongen, E.P., Borgdorff, P., Bruins, P., Kahn, R.S., Ophoff, R.A., 2013. Seasonal variation of serotonin turnover in human cerebrospinal fluid, depressive symptoms and the role of the 5-HTTLPR. *Transl. Psychiatry*. 3, e311.
- Manchia, M., Lampus, S., Chillotti, C., Sardu, C., Ardu, R., Severino, G., Del Zompo, M., 2008. Age at onset in Sardinian bipolar I patients: evidence for three subgroups. *Bipolar Disord*. 10, 443-446.
- Mansour, H.A., Monk, T.H., Nimgaonkar, V.L., 2005. Circadian genes and bipolar disorder. *Ann. Med*. 37, 196-205.
- McCarthy, M.J., Nievergelt, C.M., Kelsoe, J.R., Welsh, D.K., 2012. A survey of genomic studies supports association of circadian clock genes with bipolar disorder spectrum illnesses and lithium response. *PLoS One*. 7, e32091.
- McClung, C.A., 2007. Circadian genes, rhythms and the biology of mood disorders. *Pharmacol. Ther*. 114, 222-232.
- McClung, C.A., 2013. How might circadian rhythms control mood? Let me count the ways. *Biol. Psychiatry*. 74, 242-249.
- Molendijk, M.L., Haffmans, J.P., Bus, B.A., Spinhoven, P., Penninx, B.W., Prickaerts, J., Oude Voshaar, R.C., Elzinga, B.M., 2012. Serum BDNF concentrations show strong seasonal variation and correlations with the amount of ambient sunlight. *PLoS One*. 7, e48046.

- Morselli, P.L., Elgie, R., GAMIAN-Europe, 2003. GAMIAN-Europe/BEAM survey I-- global analysis of a patient questionnaire circulated to 3450 members of 12 European advocacy groups operating in the field of mood disorders. *Bipolar Disord.* 5, 265-278.
- NASA, 2012. Surface meteorology and Solar Energy (SSE) Release 6.0 Methodology, Version 3.1 (<http://eosweb.larc.nasa.gov/sse/>). Accessed Jan 20, 2014.
- NASA, 2010. Science Mission Directorate. The Earth's Radiation Budget. (http://missionscience.nasa.gov/ems/13_radiationbudget.html). Accessed Jan 20, 2014.
- Ortiz, A., Bradler, K., Slaney, C., Garnham, J., Ruzickova, M., O'Donovan, C., Hajek, T., Alda, M., 2011. An admixture analysis of the age at index episodes in bipolar disorder. *Psychiatry Res.* 188, 34-39.
- Pan, W., 2001. Akaike's information criterion in generalized estimating equations. *Biometrics.* 57, 120-125.
- Pergams, O.R., Zaradic, P.A., 2008. Evidence for a fundamental and pervasive shift away from nature-based recreation. *Proc. Natl. Acad. Sci. U.S.A.* 105, 2295-2300.
- Perlis, R.H., Delbello, M.P., Miyahara, S., Wisniewski, S.R., Sachs, G.S., Nierenberg, A.A., STEP-BD investigators, 2005. Revisiting depressive-prone bipolar disorder: polarity of initial mood episode and disease course among bipolar I systematic treatment enhancement program for bipolar disorder participants. *Biol. Psychiatry.* 58, 549-553.

- Petronis, A., 2003. Epigenetics and bipolar disorder: new opportunities and challenges. *Am. J. Med. Genet. C Semin. Med. Genet.* 123C, 65-75.
- Post, R.M., Leverich, G.S., Kupka, R., Keck, P. Jr., McElroy, S., Altshuler, L., Frye, M.A., Luckenbaugh, D.A., Rowe, M., Grunze, H., Suppes, T., Nolen, W.A., 2013. Increased parental history of bipolar disorder in the United States: association with early age of onset. *Acta Psychiatr. Scand.* Oct 19. doi: 10.1111/acps.12208. [Epub ahead of print]
- Roecklein, K.A., Rohan, K.J., Duncan, W.C., Rollag, M.D., Rosenthal, N.E., Lipsky, R.H., Provencio, I., 2009. A missense variant (P10L) of the melanopsin (OPN4) gene in seasonal affective disorder. *J. Affect. Disord.* 114, 279-285
- Rosa, A.R., Comes, M., Torrent, C., Sole, B., Reinares, M., Pacchiarotti, I., Salamero, M., Kapczinski, F., Colom, F., Vieta, E., 2013. Biological rhythm disturbance in remitted bipolar patients. *International Journal of Bipolar Disorders* 1, 6.
- Schürhoff, F., Bellivier, F., Jouvent, R., Mouren-Siméoni, M.C., Bouvard, M., Allilaire, J.F., Leboyer, M., 2000. Early and late onset bipolar disorders: two different forms of manic-depressive illness? *J. Affect. Disord.* 58, 215-221.
- Stedman, M.R., Gagnon, D.R., Lew, R.A., Solomon, D.H., Brookhart, M.A., 2008. An evaluation of statistical approaches for analyzing physician-randomized quality improvement interventions. *Contemp. Clin. Trials.* 29, 687-695.
- Stephenson, K.M., Schroder, C.M., Bertschy, G., Bourgin, P., 2012. Complex interaction of circadian and non-circadian effects of light on mood: shedding new light on an old story. *Sleep Med. Rev.* 16, 445-454.

- Thorne, H.C., Jones, K.H., Peters, S.P., Archer, S.N., Dijk, D.J., 2009. Daily and seasonal variation in the spectral composition of light exposure in humans. *Chronobiol. Int.* 26, 854-866.
- Tomita, T., Yasui-Furukori, N., Nakagami, T., Kaneda, A., Kaneko, S., 2012. The association between sunshine duration and paroxetine response time in patients with major depressive disorder. *J. Affect. Disord.* 136, 1067-1071.
- Tsuchiya, K.J., Byrne, M., Mortensen, P.B., 2003. Risk factors in relation to an emergence of bipolar disorder: a systematic review. *Bipolar Disord.* 5, 231-242.
- Turner, P.L., Mainster, M.A., 2008. Circadian photoreception: ageing and the eye's important role in systemic health. *Br. J. Ophthalmol.* 92, 1439-1444.
- Turner, P.L., Van Someren, E.J., Mainster, M.A., 2010. The role of environmental light in sleep and health: effects of ocular aging and cataract surgery. *Sleep Med. Rev.* 14, 269-280.
- van Bommel, W.J., 2006. Non-visual biological effect of lighting and the practical meaning for lighting for work. *Appl. Ergon.* 37, 461-466.
- van Bommel, W.J.M., van den Beld, G.J., 2004. Lighting for work: a review of visual and biological effects. *Light. Res. Technol.* 36, 255-266.
- Van Heyningen, V., Yeyati, P.L., 2004. Mechanisms of non-Mendelian inheritance in genetic disease. *Hum. Mol. Genet.* 13, Spec No 2:R225-233.
- Vandewalle, G., Collignon, O., Hull, J.T., Daneault, V., Albouy, G., Lepore, F., Phillips, C., Doyon, J., Czeisler, C.A., Dumont, M., Lockley, S.W., Carrier, J., 2013. Blue light stimulates cognitive brain activity in visually blind individuals. *J. Cogn. Neurosci.* 25, 2072-2085.

- Vandewalle, G., Gais, S., Schabus, M., Balteau, E., Carrier, J., Darsaud, A., Sterpenich, V., Albouy, G., Dijk, D.J., Maquet, P., 2007. Wavelength-dependent modulation of brain responses to a working memory task by daytime light exposure. *Cereb. Cortex.* 17, 2788-2795.
- Vasudev, A., Thomas, A., 2010. 'Bipolar disorder' in the elderly: what's in a name? *Maturitas.* 66, 231-235.
- West, K.E., Jablonski, M.R., Warfield, B., Cecil, K.S., James, M., Ayers, M.A., Maida, J., Bowen, C., Sliney, D.H., Rollag, M.D., Hanifin, J.P., Brainard, G.C., 2011. Blue light from light-emitting diodes elicits a dose-dependent suppression of melatonin in humans. *J. Appl. Physiol.* 110, 619-626.
- Whybrow, P.C., 1997. *A mood apart: Depression, mania, and other afflictions of the self.* Harper Collins/Basic Books: New York, NY.
- Wright, A., Charlesworth, B., Rudan, I., Carothers, A., Campbell, H., 2003. A polygenic basis for late-onset disease. *Trends Genet.* 19, 97-106.
- Zaidi, F.H., Hull, J.T., Peirson, S.N., Wulff, K., Aeschbach, D., Gooley, J.J., Brainard, G.C., Gregory-Evans, K., Rizzo, J.F. 3rd, Czeisler, C.A., Foster, R.G., Moseley, M.J., Lockley, S.W., 2007. Short-wavelength light sensitivity of circadian, pupillary, and visual awareness in humans lacking an outer retina. *Curr. Biol.* 17, 2122-2128.
- Zeger, S.L., Liang, K.Y., 1986. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 42, 121-130.

Table 1. Patient onset location by latitude

Degrees latitude (north and south)*	Number of patients
0-9	309
10-19	200
20-29	286
30-39	1222
40-49	1475
50-59	297
60-69	247
70-79	1
Total	4037

* 1043 in southern hemisphere.

Table 2. Estimated parameter coefficients explaining age of onset with all patients*

				99% Confidence interval		Coefficient significance	
	Parameter	Coefficient estimate	Standard error	Lower	Upper	Wald Chi-square	P
Model 1 N=3334 **							
	Maximum monthly increase in solar insolation	-4.862	1.496	-8.678	-0.973	10.412	0.001
	No family history X maximum monthly increase in solar insolation	2.310	0.311	1.510	3.110	55.271	< 0.001
Model 2 N=3600 ***							
	Maximum monthly increase in solar insolation	-4.948	1.732	-9.409	-0.487	8.161	0.004
	First episode manic X maximum monthly increase in solar insolation	1.663	0.400	0.633	2.694	17.301	< 0.001

* GEE model estimated age of onset using a constant, the country of onset median age, birth cohort groups and the listed parameters with an exchangeable correlation structure in each cluster. The Wald hypothesis test degrees of freedom were 1 for all models.

** 256 onset locations. All Sidak pairwise mean age of onset comparisons for birth cohort and family history were significantly different at the < 0.001 level.

*** 265 onset locations. All Sidak pairwise mean age of onset comparisons for birth cohort and family history were significantly different at the < 0.001 level.

Table 3. Estimated parameter coefficients explaining age of onset with patients born after 1959*

					99% Confidence interval		Coefficient significance	
	Parameter	Coefficient estimate	Standard error		Lower	Upper	Wald Chi-square	P
Model 1 N= 2091 **								
	Maximum monthly increase in solar insolation	-4.623	1.407		-8.247	-0.998	10.792	0.001
	No family history X maximum monthly increase in solar insolation	1.809	0.265		1.127	2.492	46.622	< 0.001
Model 2 N= 2271 ***								
	Maximum monthly increase in solar insolation	-4.880	1.429		-8.561	-1.199	11.661	0.001
	First episode manic X maximum monthly increase in solar insolation	2.213	0.337		1.345	3.081	43.129	< 0.001

* GEE model estimated age of onset using a constant, the country of onset median age and the listed parameters with an exchangeable correlation structure in each cluster. The Wald hypothesis test degrees of freedom were 1 for all models.

** 216 Onset Locations.

*** 223 Onset Locations.

Table 4. Mean adjusted age of onset by maximum monthly increase in solar insolation (kWh/m²/day) groups

Maximum monthly increase in solar insolation (kWh/m ² /day)	Mean adjusted age of onset	Number of onset reference sites	Number of patients	Percent of patients	Example Locations	Latitude (degrees)
< 0.75	27.53	22	779	19%	Kuala Lumpur, Malaysia Medellin, Columbia Bangalore, India Salvador, Brazil Hong Kong, China Tokyo, Japan	3.17 N 6.29 N 12.98 N 12.98 S 22.25 N 35.69 N
≥ 0.75 and < 1.0	22.47	47	133	3%	Kedah, Malaysia Kolar, India Miami, FL, US Princeton, NJ, US Boston, MA, US	6.13 N 13.13 N 25.78 N 40.35 N 42.35 N
≥ 1.0 and < 1.25	20.97	136	1756	44%	Porto Alegre, Brazil San Diego, CA, US Buenos Aires, Argentina Melbourne, Australia Thessaloniki, Greece Barcelona, Spain Siena, Italy Rochester, MN, US Nova Scotia, Canada Vienna, Austria Paris, France Wurzburg, Germany	30.03 S 32.71 N 34.60 S 37.81 S 40.64 N 41.38 N 43.32 N 44.02 N 45.10 N 48.20 N 48.87 N 49.79 N
≥ 1.25 and < 1.5	20.82	85	707	18%	Beer Sheva, Israel Valparaiso, Chile San Francisco, CA, US	31.25 N 33.05 S 37.78 N

19.32	28	662	16%	Cape
				Loss
				A
				H
				Tr
	318	4037	100%	

Figure 1. Comparison of monthly solar insolation pattern at northern, equatorial and temperate latitudes. The pattern of monthly solar insolation at Helsinki, Finland (60.2 N), San Francisco, CA, US (37.8 N) and Medellin, Columbia (6.3 N).

Accepted manuscript

Conflict of Interest

MB is a consultant for Alkermes, AstraZeneca, BristolMyers Squibb, Ferrer Internacional, Janssen, Lilly, Lundbeck, Otsuka, Servier, Takeda, has received speaker honoraria from AstraZeneca, BristolMyers Squibb, GlaxoSmithKline, Lilly, Lundbeck, Otsuka, Pfizer, and has received grant/research support from The Stanley Medical Research Institute, NARSAD, Deutsche Forschungsgemeinschaft, European Commission (FP7), American Foundation for Suicide Prevention, Bundesministerium für Bildung und Forschung (BMBF). OAA has received speaker honoraria from GSK, Lundbeck, and Otsuka. M Berk has been a speaker for Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck, Merck, Pfizer, Sanofi Synthelabo, Servier, Solvay and Wyeth, served as a consultant to Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck Merck and Servier, and has received Grant/Research Support from the NIH, Cooperative Research Centre, Simons Autism Foundation, Cancer Council of Victoria, Stanley Medical Research Foundation, MBF, NHMRC, Beyond Blue, Rotary Health, Geelong Medical Research Foundation, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Meat and Livestock Board, Organon, Novartis, Mayne Pharma, Servier and Woolworths. SD has received advisory board fees and speaker honoraria from Eli Lilly, conference travel support from Servier, and has received Grant/Research Support from the Stanley Medical Research Institute, NHMRC, Beyond Blue, ARHRF, Simons Foundation, Geelong Medical Research Foundation, Fondation FondaMental, Eli Lilly, Glaxo SmithKline, Organon, Mayne Pharma and Servier. AF is/has been a consultant or speaker or has received

research support or has participated in symposia sponsored by Angelini, Astra Zeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Janssen, Lundbeck, Mediolanum Pharm, Novartis, Otsuka, Pfizer, and Roche. MAF has received grants from Pfizer, Myriad, National Institute of Mental Health (NIMH), National Institute of Alcohol Abuse and Alcoholism (NIAAA), and the Mayo Foundation, and received travel support from GlaxoSmithKline. AGP has received grants and served as consultant, advisor or CME speaker for Almirall, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, Glaxo-Smith-Kline, Janssen-Cilag, Jazz, Johnson & Johnson, Lundbeck, Merck, Otsuka, Pfizer, Sanofi-Aventis, Servier, Shering-Plough, Solvay, the Spanish Ministry of Science and Innovation (CIBERSAM), the Ministry of Science (Carlos III Institute), the Basque Government, the Stanley Medical Research Institute, and Wyeth. FK has been a member of the board of speakers for Astra-Zeneca, Eli Lilly, Janssen and Servier, a consultant for Servier, and received grants/research support from Astra-Zeneca, Eli Lilly, Janssen-Cilag, Servier, CNPq, CAPES, NARSAD and Stanley Medical Research Institute. UL has received speaker honoraria from AstraZeneca and Lundbeck, has received research grants from Dalhousie University, Halifax, Canada and from the German Federal Ministry of Education and Research. CL has received grants from Novartis, Janssen, Covance-Takeda and of COLCIENCIAS and University of Antioquia financial strategy. FGN held a temporary position as an Associate Medical Advisor for Eli Lilly & Co from June 2012 to May 2013. CO served as consultant for Lundbeck, Sunovion, BMS, and has received speaker honoraria from Lundbeck and BMS. AP has received research support from AstraZeneca, and received speaker honoraria from AstraZeneca and Lundbeck. NR is a consultant for Takeda Pharmaceuticals and has

received research support from Bayer Pharmaceuticals, ADA (American Diabetes Association) and Corcept Pharmaceuticals. AR participated in trials sponsored by Astra Zeneca. AMS has received speaker honoraria from Astra Zeneca, Pfizer and Abbott and received financial support from the Program of Mood and Anxiety Disorders CETHA Federal University of Bahia. DS has received research grants and/or consultancy honoraria from Biocodex, Lundbeck, Novartis, Servier, and Sun. SS was/is a consultant for Glaxo Smith Kline, Astra Zeneca and Abbott and has received speaker honoraria from Abbott, Astra Zeneca, Lilly, GSK and Janssen. EV has received grants and served as consultant, advisor or CME speaker for Adamed, Alexza, Almirall, AstraZeneca, Bial, Bristol-Myers Squibb, Elan, Eli Lilly, Ferrer, Forest Research Institute, Gedeon Richter, Glaxo-Smith-Kline, Janssen-Cilag, Jazz, Johnson & Johnson, Lundbeck, Merck, Novartis, Organon, Otsuka, Pfizer, Pierre-Fabre, Qualigen, Roche, Sanofi-Aventis, Servier, Shering-Plough, Shire, Solvay, Sunovion, Takeda, Teva, United Biosource Corporation, and Wyeth. MA, EA, RA, CB, FB, RB, RHB, TDB, LB, YB, EYWC, MDZ, BE, KNF, JGF, TG, HH, SH, CH, AI, ETI, SK, BK, RK, MK, BL, ERL, CLJ, GM, MM, WM, SM, MMC, IM, GM, RM, CO, YO, DQ, RR, PR, JKR, KS, ES, CS, AHS, KS, HT, YT, CT, BV, MJW, MZ, and PCW have no conflict of interest to declare.

Role of Funding Sources

This work at was funded in part by the Canadian Institutes of Health Research (MA, grant number 64410); the Research Council of Norway (OAA grant numbers 213837; 223273; 217776); South-East Norway Health Authority (OAA, grant number 2013-123); KG Jebsen Foundation (OAA); a NHMRC Senior Principal Research Fellowship (M Berk, grant number 1059660); INSERM (BE, grant number C0829) and APHP (BE, grant number AOR11096); the Spanish Government (AGP, grant numbers PS09/02002 CIBER Network; EC10-333, PI10/01430, PI10/01746, PI11/01977, PI11/02708, 2011/1064, 11-BI-01, 1677-DJ-030, EC10-220); European Regional Development Funds and local grants from the Basque Country Government (AGP, MMC, grant numbers 2008111010, 2009111047, 2010111170, 2010112009, 2011111110, 2011111113, SAIO10-PC10BF01, SAIO11-PE11BF006, SAIO11-PE11BF007, SAIO10-PR10BF01, GIC 10/80, KRONIK 11/010); the Basque Foundation for Health Innovation and Research (AGP, MMC, grant numbers BIOEF; BIO09/EM/010); the Spanish Clinical Research Network (AGP, MMC, grant numbers CAIBER; 1392-D-079) and the University of the Basque Country (AGP, MMC, grant numbers GIC10/80, US10/08, EHU08/54); Stanley Research Foundation (APG, MMC, grant number 03-RC-003); the Research Council of Norway (IM, grant numbers ES488722 , ES421716); the Regional Health Authority of South Eastern Norway (IM, grants number 2011085, 2013088); St Olavs University Hospital, Trondheim, Norway (GM); DFG (AR, grant numbers SFB TRR 58, B06, Z02); the DFG and Länder funds (AR, grant number RTG1252/2); Medical Research Council of South Africa (DS); Spanish Ministry of Economy and

Competitivity (EV, grants number PI12/00912, PN 2008-2011; the Instituto de Salud Carlos III- Subdirección General de Evaluación y Fomento de la Investigación (EV); Fondo Europeo de Desarrollo Regional Unión Europea. Una manera de hacer Europa (EV); CIBERSAM (EV); the Comissionat per a Universitats i Recerca del DIUE de la Generalitat de Catalunya to the Bipolar Disorders Group (EV, grant number 2009 SGR 1022). MB, EA, RA, CB, FB, RB, RHB, TDB, LB, YB, EYWC, MDZ, SD, AF, MAF, KNF, JGF, TG, HH, SH, CH, AI, ETI, FK, SK, BK, RK, MK, BL, ERL, CLJ, UL, GM, MM, WM, SM, RM, FGN, CO, YO, AP, DQ, RR, NR, PR, JKR, KS, AMS, ES, CS, SS, AHS, KS, HT, YT, CT, BV, MJW, MZ and PCW have no specific funding to acknowledge. The funding sources had no involvement in the study design, collection, analysis and interpretation of data, in writing the report, and in the decision to submit for publication.

Contributors

All authors contributed to and approved the final manuscript. Authors MB and TG designed the study. Authors MA, OAA, EA, RA, FB, RHB, MB, TDB, LB, EYWC, MDZ, SD, BE, AF, MAF, KNF, JC, JGF, AGP, HH, SH, CH, AI, ETI, FK, SK, BK, RK, MK, BL, ERL, UL, CLJ, GM, MM, WM, MMC, IM, GM, RM, FGN, CO, YO, AP, DQ, RR, NR, AR, PR, JKR, KS, AMS, CS, DS, SS, AHS, KS, HT, YT, CT, EV, BV, MJW and MZ were involved with data collection. Author TG provided data analysis. Authors MB and TG were involved in the draft manuscript. Author PCW was involved in the initial review.

Acknowledgements

We would like to thank the International Society of Bipolar Disorders for supporting this project.

Accepted manuscript

Figure 1. Comparison of monthly solar insolation pattern at northern, equatorial and temperate latitudes. The pattern of monthly solar insolation at Helsinki, Finland (60.2 N), San Francisco, CA, US (37.8 N) and Medellin, Columbia (6.3 N).

Accepted manuscript

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Bauer, M;Glenn, T;Alda, M;Andreassen, OA;Angelopoulos, E;Ardau, R;Baethge, C;Bauer, R;Bellivier, F;Belmaker, RH;Berk, M;Bjella, TD;Bossini, L;Bersudsky, Y;Cheung, EYW;Conell, J;Del Zompo, M;Dodd, S;Etain, B;Fagiolini, A;Frye, MA;Fountoulakis, KN;Garneau-Fournier, J;Gonzalez-Pinto, A;Harima, H;Hassel, S;Henry, C;Iacovides, A;Isometsa, ET;Kapczinski, F;Kliwicksi, S;Koenig, B;Krogh, R;Kunz, M;Lafer, B;Larsen, ER;Lewitzka, U;Lopez-Jaramillo, C;MacQueen, G;Manchia, M;Marsh, W;Martinez-Cengotitabengoa, M;Melle, I;Monteith, S;Morken, G;Munoz, R;Nery, FG;O'Donovan, C;Osher, Y;Pfennig, A;Quiroz, D;Ramesar, R;Rasgon, N;Reif, A;Ritter, P;Rybakowski, JK;Sagduyu, K;Scippa, AM;Severus, E;Simhandl, C;Stein, DJ;Strejilevich, S;Sulaiman, AH;Suominen, K;Tagata, H;Tatebayashi, Y;Torrent, C;Vieta, E;Viswanath, B;Wanchoo, MJ;Zetin, M;Whybrow, PC

Title:

Relationship between sunlight and the age of onset of bipolar disorder: An international multisite study

Date:

2014-10-01

Citation:

Bauer, M., Glenn, T., Alda, M., Andreassen, O. A., Angelopoulos, E., Ardu, R., Baethge, C., Bauer, R., Bellivier, F., Belmaker, R. H., Berk, M., Bjella, T. D., Bossini, L., Bersudsky, Y., Cheung, E. Y. W., Conell, J., Del Zompo, M., Dodd, S., Etain, B., ... Whybrow, P. C. (2014). Relationship between sunlight and the age of onset of bipolar disorder: An international multisite study. JOURNAL OF AFFECTIVE DISORDERS, 167, pp.104-111. <https://doi.org/10.1016/j.jad.2014.05.032>.

Persistent Link:

<http://hdl.handle.net/11343/43870>