HHS Public Access

Author manuscript

J Clin Psychiatry. Author manuscript; available in PMC 2016 February 01.

Published in final edited form as:

J Clin Psychiatry. 2015 February ; 76(2): 128–134. doi:10.4088/JCP.14m08981.

Seasonality shows evidence for polygenic architecture and genetic correlation with schizophrenia and bipolar disorder – a meta-analysis of genetic studies

Enda M Byrne, PhD[1,2], **Uttam Raheja, MD**[3,4], **Sarah H. Stephens, PhD**[5], **Andrew C Heath, DPhil**[6], **Pamela AF Madden, PhD**[6], **Psychiatric Genetics Consortium Major Depressive Disorder Working Group**[*], **Dipika Vaswani, MD**[3], **Gagan V. Nijjar, MD**[3,7], **Kathleen A. Ryan, MS**[5], **Hassaan Youssufi**[3], **Philip R Gehrman, PhD**[8], **Alan R Shuldiner, MD**[5,9], **Nicholas G Martin, PhD**[2], **Grant W Montgomery, PhD**[2], **Naomi R Wray, PhD**[1], **Elliot C Nelson, MD**[6], **Braxton D Mitchell, PhD**[5,9], and **Teodor T Postolache, MD**[3,4,10,11]

[1]The University of Queensland, Queensland Brain Institute, St. Lucia, QLD 4072, Australia

[2]Queensland Institute of Medical Research, 300 Herston Road, Herston, QLD 4029

[3]Mood and Anxiety Program, Department of Psychiatry, University of Maryland School of Medicine, Baltimore, Maryland, USA

[4]Saint Elizabeths Hospital, Psychiatry Residency Training Program, Washington, DC, USA

[5]Division of Endocrinology, Diabetes and Nutrition, Department of Medicine, University of Maryland School of Medicine, Baltimore, MD, USA

[6]Department of Psychiatry, Washington University, St.Louis, MO, USA

[7]Department of Psychiatry, Kaiser Permanente, Santa Rosa CA

[8]Behavioral Sleep Medicine Program, Department of Psychiatry & Penn Sleep Center, University of Pennsylvania, Philadelphia, USA

[9]Geriatric Research and Education Clinical Center, Veterans Administration Medical Center, Baltimore, MD, USA

[10]Division of Child and Adolescent Psychiatry & University of Maryland Child and Adolescent Mental Health Innovations Center, University of Maryland School of Medicine, Baltimore, MD, USA

[11]National Center for the Treatment of Phobias, Anxiety and Depression, Washington, DC, USA

Abstract

Objective—To test common genetic variants for association with seasonality (seasonal changes in mood and behavior) and to investigate whether there are shared genetic risk factors between psychiatric disorders and seasonality.

Correspondence to: Enda Byrne, The University of Queensland, Queensland Brain Institute, Upland Road, St.Lucia, QLD 4072, Brisbane, Australia, enda.byrne@uq.edu.au, Phone: +61 7 33466414, Fax: +61 7 3346 6301.

[*]PGC contributors and affiliations are listed in the Supplementary eTable 1

Conflict of Interest Statement; All authors have no conflicts of interest to declare

Methods—A meta-analysis of genome-wide association studies (GWAS) conducted in Australian and Amish populations in whom the Seasonal Pattern Assessment Questionnaire (SPAQ) had been administered. The total sample size was 4,156 individuals. Genetic risk scores based on results from prior large GWAS studies of bipolar disorder (BD), major depressive disorder (MDD), and schizophrenia (SCZ) were calculated to test for overlap in risk between psychiatric disorders and seasonality.

Results—The most significant association was with rs11825064 ($p = 1.7 \times 10^{-6}$, $\beta = 0.64$, S.E = 0.13), an intergenic SNP found on chromosome 11. The evidence for overlap in risk factors was strongest for SCZ and seasonality, with the SCZ genetic profile scores explaining 3% of the variance in log-transformed GSS. BD genetic profile scores were also significantly associated with seasonality, although at much weaker levels, and no evidence for overlap in risk was detected between MDD and seasonality.

Conclusions—Common SNPs of very large effect likely do not exist for seasonality in the populations examined. As expected, there was overlapping genetic risk factors for BD (but not MDD) with seasonality. Unexpectedly, the risk for SCZ and seasonality had the largest overlap, an unprecedented finding that requires replication in other populations, and has potential clinical implications considering overlapping cognitive deficits in seasonal affective disorders and SCZ

Introduction

Although seasonal changes in mood and behavior (seasonality) have been recognized for a long time[1], seasonal affective disorder (SAD) was first defined by Rosenthal et al.[2] as a syndrome with recurrent depression in fall and winter and alleviation of depressive symptoms in spring and summer. In addition, while SAD is not a distinct clinical entity in the fourth and fifth iterations of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), these manuals include a longitudinal seasonal pattern specifier for major depressive episodes with a consistent temporal relationship with specific times of the year, such as fall and winter, in the past two years in individuals with recurrent Major Depressive Disorder (MDD) and Bipolar I or II Disorder (BD), with the depressive episodes undergoing full remission or, less commonly, a switch to hypomanic or manic symptoms at others times of the year such as spring or summer[3–5] Rosenthal[5] (2009) has argued from many lines of evidence that SAD should be considered an independent clinical entity rather than a seasonal mood specifier. SAD is characterized by symptoms of depression such as changes in sleep pattern, fluctuations in weight, decreased energy, and reduced social activities at a particular period of the year, followed by at least partial remission when the season changes[6]. The most common form is SAD with a winter depression pattern (SAD).[2] SAD symptoms are particularly responsive to bright light treatment.[7,8,9,10] Contrary to common expectations, SAD patients can manifest severe symptomatology[11],[12], and cognitive deficits[12], similar to nonseasonal depression..[12] SAD as a clinical diagnosis represents the extreme of a spectrum of seasonality that exists in the population. Many individuals experience seasonal changes in mood and behavior at subclinical levels that can cause significant distress and impairment[13, 14], while others may experience only very subtle changes[15].

Family studies of SAD prevalence report increased prevalence of SAD in first-degree relatives of SAD patients[16, 17]. A previous analysis of a large epidemiological twin study[18],

a subset of which is included in genetic analyses of our data, estimated that genetic factors account for 29% of the overall variance in seasonality in men and women as assessed by the Seasonal Pattern Assessment Questionnaire (SPAQ)[19].

Family studies have also shown increased prevalence of nonseasonal depression in the families of SAD cases, but the question of whether seasonality and depression are distinct in terms of the genetic risk factors that predispose to them remains unanswered[15].

There are differences between MDD with seasonal pattern and BD with seasonal pattern, for instance, the recurrence of the seasonal depression and severity of the course, with higher rates of hospitalization in the bipolar form[20]. Importantly, even the unipolar form of SAD has been previously conceptualized clinically as belonging to the bipolar spectrum[21].

While a number of candidate gene analyses of SAD have been performed,[22–27], no consistently replicable findings have been gleaned from candidate gene studies of SAD.

Genome-wide association studies (GWAS) have been successful in mapping genetic variants that increase risk to schizophrenia (SCZ)[28, 29] and BD[30], however, large sample sizes have been required to detect them. No GWAS studies have as yet been performed for SAD.

Furthermore, the molecular genetics era has given valuable insights into the etiology of psychiatric disorders that may influence diagnosis in the future. For example, it has recently been demonstrated that much of the genetic risk is shared between psychiatric disorders[31].

The aim of this study is to perform a GWAS of seasonality in a population of Australian twins and an Old Order Amish population from Lancaster county, Pennsylvania and to investigate the genetic overlap between seasonality and three psychiatric disorders – major depressive disorder (MDD), disorder (BD), and schizophrenia (SCZ).

Methods

Seasonal Pattern Assessment Questionnaire (SPAQ)

A well-studied SAD screening and research questionnaire, the SPAQ[32] evaluates SAD by estimating a score of global seasonality (GSS) calculated by responses on a Likert scale of 0–4 for each of six indices of seasonality, the degree of to which these changes cause impaired functioning (the problem scale, ranging from 0–5), and the season(s) indicated by the participant as representing the time during which they feel “worst.” For cases with incomplete responses on the GSS indices, the GSS was estimated from the proportion of responses.

QIMR

Participants were drawn from two studies conducted at the Queensland Institute of Medical Research (QIMR). The first study, which is described previously[18], involved mailing a questionnaire that included the SPAQ to 3,808 twin pairs from the Australian Twin Registry. A total of 2,487 twin pairs and 687 singletons returned questionnaires with responses to the SPAQ. A total of 2,605 individuals provided both genetic and phenotypic information.

The Midwest Alcohol Research Centre study is a collaborative study between investigators at QIMR and Washington University in St. Louis, Missouri, USA, that was initiated to investigate the effects of severe childhood and adult trauma on alcohol consumption and alcohol dependence. The target sample (N=3,607 individuals) had previously participated in a GWAS of these alcohol-related outcomes (Heath et al., 2011). Participants undertake a phone interview with a trained interviewer with the aim of assessing lifetime history of severe childhood and adult environmental stressors. The SPAQ was included as part of the protocol. At the time of analysis, a total of 686 individuals had completed an interview and provided responses to the SPAQ. After removal of ancestry outliers, a total of 664 individuals provided both phenotype and genotype information.

The overall sample size for inclusion in the GWAS was 3,269. The total sample providing phenotypic information was 6,347. All participants gave informed consent and the study was approved by the ethics board of QIMR. Descriptive statistics are given in Table 1.

In the interest of reducing the multiple testing statistical burden, it was decided to analyze the global score and not the symptoms individually.

As the Australian twin sample was recruited from different regions of the country, a state of residence fixed effect was included in a linear model along with age and sex, and the residuals of the GSS scores after adjusting for these effects were tested for association. GSS scores from all phenotyped individuals were used to extract the residuals.

Genotyping

Full details of the genotyping, imputation and QC procedures are given in the Supplementary Material. After genotyping QC and imputation, a total number of 2,380,486 SNPs were included.

Amish—Participants in the study were Amish individuals enrolled in community-based studies conducted at the University of Maryland and University of Maryland's Amish Research Clinic in Lancaster County, Pennsylvania[33–36], who had consented to be contacted for future studies. Seasonal Pattern Assessment Questionnaires (SPAQ) were sent by mail to 2,260 such Amish individuals, both male and female, and all above the age of 18 years. The letter contained, in addition to the SPAQ, a statement that completion of the SPAQ implied documented informed consent for the study and directions on completion of the questionnaire. This protocol was approved by the Institutional Review Board of the University of Maryland. Initial mailings were done in May, 2010. A subsequent mailing was done for those who had not responded to the initial mailing in September 2010. All responses received before December 31, 2011, numbering a total of 1,306 (response rate 57.8%), comprised the dataset.

Using a convenience subsample of 68 subjects administered the SPAQ twice over a 4 month period, the test-retest reliability of the GSS and problem rating score (PRS) in the Amish was adequate using Cronbach's alpha (GSS, $\alpha = 0.87$; PRS, $\alpha = 0.79$)[37] and comparable to that in the general population[38]

Genotyping

Genotyping was performed using the Affymetrix GeneChip® Human Mapping 500K or 6.0 Array set (Affymetrix, Santa Clara, CA, USA). Genotype calls were made using the BRLMM genotype calling algorithm. A total of 364,336 informative autosomal SNPs that passed quality-control were included in the analysis. MACH[39] (Markov-Chain Haplotyper) was used for imputation (Release22, Build36) after applying the following exclusion filters: 1) not in HapMap; 2) frequency < 0.01; 3) Hardy-Weinberg p-value < 1×10^{-6}; 4) missingness > 0.05.

Association Analysis

Association testing in the Australian sample was performed in MERLIN[40, 41], using the dosage scores from the imputation. MERLIN accounts for the relationship between individuals in the sample. Four ancestry principal components were included as covariates to correct for population stratification. Prior to this, those individuals with evidence of non-European ancestry were removed from the analysis.

Association analysis in the Amish sample was performed using Mixed Models Analysis for Pedigrees and Populations (MMAP) software developed by J.R. O'Connell (http://edn.som.umaryland.edu/mmap/index.php) that accounts for family structure by conditioning the association of genotype with outcome on the relationship matrix (included as a random effect) and covariates (e.g., age and sex). Meta-analysis was performed using the inverse variance weighting method in METAL[42].

Statistical Power

We simulated a trait with a heritability of 0.29 using MERLIN and estimated the statistical power to detect a variant with a MAF 0.2 that explains 1% of the phenotypic variance in GSS. The Australian sample has 50.8% power to detect such a variant at the genome-wide significance threshold. The sample has 89% power to detect a variant explaining 1.5% of the phenotypic variance.

Profile Scoring

In the Australian dataset, we tested whether there is a genetic correlation between seasonality, measured by the GSS, and mood disorders, utilizing the results from the Psychiatric GWAS Consortium (PGC) GWAS analyses of SCZ[28], BD[30], and MDD[43] to generate genetic profile scores. A single twin from each pair was selected at random for analysis so as to exclude relatives so that the analysis set included 1,999 unrelated individuals. For each individual, three separate profile scores were generated based on the results from the PGC GWASs. The profile scoring methodology generates a single genetic "load" score for each individual by weighting each SNP by the log of the odds ratio estimated in the original study. In this way, SNPs with a larger predicted effect on risk to disease are given more weight in making the predictor. Linear regression of the profile score on the trait of interest allows for estimation of how well the profile score predicts the phenotype. This method was first described in[44] and used to demonstrate that there is overlap in the genetic risk factors for SCZ and BD.

We used the summary results from the PGC BD and SCZ GWAS analyses separately (downloaded from http://pgc.unc.edu). The SCZ study included 9,394 cases and 12,462 controls and the BIP study included 7,481 cases and 9,250 controls. These results had been clumped at $r^2 < 0.25$ to ensure that only the most significant SNP in a given LD block is included in the analysis and the same association signal is not included more than once. We also generated profile scores using association results from PGC MDD[43]. However, since samples from QIMR contribute to PGC MDD analysis, the PGC MDD data were re-analysed with the Australian samples excluded, so as to remove any chance of overlap between the discovery and target samples. A total of 7790 cases and 7808 controls were included in the revised PGC MDD analysis. The results from this GWAS analysis were used in the MDD profile score analysis.

Results

Genome-wide Association Study

Results from the most significantly associated SNPs ($p < 10^{-5}$) from the Australian sample are shown in Supplementary eTable 2. No SNPs reached genome-wide significance in the initial genome-wide association study. All independent SNPs $r^2 < 0.5$ or >50kb distance apart with ($p < 10^{-4}$) were tested for replication in the Amish sample. No SNPs passing the significance threshold in the Australian sample were replicated in the Amish with nominal significance ($p < 0.05$).

A total of 2,354,422 markers that were in common between the two studies were included in a meta-analysis of the two individual studies. No genes reached the genome-wide significant threshold ($p < 5 \times 10^{-8}$). The most significant SNP in the meta-analysis was rs11825064 ($p = 1.7 \times 10^{-6}$, $\beta = 0.64$, S.E = 0.13), an intergenic SNP found on chromosome 11. A list of the most significant results is provided in Supplementary eTable 3. A description of the GWAS results, meta-analysis, in addition to results from analyses to estimate the heritability explained by all SNPs are reported in the Supplementary Material. Q-Q plots for each of the GWAS analyses are shown in Supplementary eFigures 1–3 and a Manhattan Plot of the results is shown in Supplementary eFigure 4.

Genetic Overlap using Profile Scoring

The results for the profile score analysis for all three disorders are shown in Supplementary eTable 4. The results for BD and SCZ are also shown in Figure 1. There is very strong evidence for genetic overlap between SCZ and seasonality ($p < 1 \times 10^{-15}$ for genetic scores based on SNPs associated with SCZ at $p < 0.5$ or all SNPs) and milder evidence for genetic overlap between BD and seasonality ($p = 0.004 – 0.005$ for genetic scores based on SNPs associated with SCZ at $p < 0.1$, $p < 0.5$, or all SNPs). The genetic risk score for SCZ accounted for up to 3.1% of the phenotypic variation in GSS. A nominally significant proportion of the variance in the GSS is explained by 427 SNPs with $p < 0.001$ from the PGC SCZ GWAS ($p = 0.0018$, variance explained = 0.4%). The null hypothesis that the variance explained by all the SCZ SNPs is zero is rejected ($p = 1.53 \times 10^{-15}$). In contrast, genetic risk score for BD accounted for only 0.4% of the phenotypic variation in GSS (see Supplementary eTable 4). No evidence for genetic overlap between MDD and seasonality

was observed, as the amount of variance in GSS explained by the MDD polygenic scores was not significantly different from zero.

Discussion

We performed a meta-analysis of two GWAS of the GSS derived from the SPAQ in a sample of twins from Australia and members of the Amish community in Pennsylvania. No genome-wide significant loci were detected. The results of gene mapping studies in other affective disorders indicate that a polygenic model, with many common alleles of small effect influencing risk, is likely to explain a substantial proportion of their heritability[28, 44–46]. Our results suggest that common variants associated with seasonality and that have unusually large effects sizes are unlikely to exist. While the lack of power is a severe limitation of our study, our results will be useful for future meta-analyses of seasonality and SAD, and provide a list of candidates that can be tested in other cohorts.

The differences between the two populations included in this study may have also increased the chances of negative findings. The geographical differences between Australia and the north-east of the United States are substantial, and there are differences between the amount of sunshine and the day length in different seasons. Even within Australia, there is great variability in day length between cities. We have tried to account for these differences by including state as a covariate in the analysis, however subtle differences may still exist.

Genetic differences between the populations also exist. The Amish are a genetically isolated population who may harbor unique genetic variants that predispose to seasonality that will not be detected in studies that include other populations. The heritability of seasonality was estimated to be 13.6% in the Old Order Amish[38], somewhat lower than the estimate in the Australian population-based sample. This indicates that genetic differences between individuals contribute less to the overall variance of seasonality in the Old Order Amish than in Australians. Furthermore, the prevalence of SAD in the Amish is the lowest of all Caucasian populations that have been assessed using the SPAQ. This implies that the Amish population is relatively resilient to seasonality. The profile scoring analyses were performed only in the Australian population and may therefore not be generalizable to the Amish. However, performing the overlap analysis in the Amish lacks validity, and the Amish appear to have a very low prevalence of schizophrenia, a likely founder effect (unpublished observation).

A further limitation of our study is that it did not include actual diagnosis of mental conditions. This would have permitted the exclusion of those with a psychiatric diagnosis prior to the profile scoring, and therefore the ability to test for genetic overlap between these disorders and seasonality in those without another psychiatric comorbidity. The sample used for profile scoring is a population-based twin sample, so the prevalence of severe psychiatric disorders is likely to be low.

It is noteworthy that genetic profile scores generated from the SCZ GWAS explain more variance in seasonality than those derived from the BD and MDD studies. This result is surprising given that seasonal pattern can be added as a modifier of a unipolar and bipolar

depression diagnosis in DSM 5. In contrast, the seasonal pattern is not clinically or epidemiologically considered in association with SCZ. The finding that the SCZ profile scores explain a larger proportion of variance in the GSS, may be due to differences between the GWAS studies from which the polygenic scores were generated. For instance, a larger sample size, or better accuracy of diagnosis or lack of some other confounding source could lead to more accurate estimates of the true SNP effects in the SCZ GWAS compared to those of BD or MDD. Summing more accurate SNP effect estimates of over thousands of SNPs could lead to substantially more accurate polygenic scores.

In contrast to BD, MDD showed no evidence for genetic overlap with GSS in our sample. Conceptually, SAD has been considered as a condition on the spectrum of bipolarity[21], even if major depression episodes alternate with periods of remission. To date, GWASs of MDD have failed to uncover any replicable common variants. One possible reason why this is the case is that the accuracy of the estimates of the SNP effects from the MDD GWAS may be less accurate than from the SCZ and BD GWAS studies. It has been argued that a GWAS of MDD has less power than the GWAS of SCZ or BD for GWAS of the same sample size, simply reflecting that MDD is a more prevalent disorder, potentially more heterogenous, and with a lower proportion of the risk explained by genetic factors[47].

To our knowledge, this is the first time that direct evidence at the molecular level has been provided for the overlap between seasonality and BD that has been previously suggested clinically[21].

Although seasonality of mood and general health has been observed since ancient times, seasonality of psychiatric symptoms (predominantly affective, but also psychotic and catatonic features as well as cognitive deficits), was clinically described in the early 19th century by Pinel and his student Esquirol, with additional early contributions by Griesinger, Kraepelin, and Kraines (reviewed by Wehr and Rosenthal 1989[1]). To our knowledge, our current report provides for the first time a direct evidence at the molecular for an overlap that has been previously suggested clinically[21].

While the association between seasonality of mood and SCZ was unexpected, a hint of a relationship was reported in small samples at high latitudes[48]. Specifically, Doorack et al (2007) examined SAD symptoms in schizophrenia patients in Alaska and found that 36% of patient with schizophrenia had co-occurring SAD. Moreover, studies previous studies have suggested an association between onset of the first episode of schizophrenia and season (e.g., Strous et al, 2001[49]). Additionally, studies conducted in the Northern Hemisphere found a summer peak of schizophrenia admissions in hospitals[50–52]. In England and Wales, for example, Hare and Walter (1978)[51] found a summer peak of schizophrenia admissions. Clarke et al (1998)[53] found a seasonal association in first episode schizophrenia admissions in Ireland, although this association varied on an annual basis. In a subsequent study, Clarke et al (1999)[54] found that the seasonal association only held for first admissions and not for subsequent admissions. Shiloh et al (2005)[55] found a summer peak for schizophrenia admissions in Israel. In China, Tian et al (2006)[55] found a spring peak (March) in schizophrenia admissions, although they noted that they did not distinguish between first episodes and readmission, which, according to Clarke et al (1999)[54], may be necessary to

isolate seasonality effects. However, there are studies that found no seasonal variation in schizophrenia, or that founds patterns contrary to those previously reported. For example, Aviv et al (2011)[54], as well as Amr and Volpe (2012)[56] did not find any seasonal effect on admission rates. In the Southern Hemisphere, Davies et al. (2000)[57] found a peak in first episode schizophrenia admission in the winter (August), similar to Owens and McGorry (2003)[58]. In contrast, Daniels et al (2000)[59] did not find a seasonal association in Tasmania with admission with diagnoses of schizophrenia and bipolar disorder.

There is a certain clinical symptoms that overlap between SAD and SCZ, including cognitive deficits, social withdrawal, and changes in sleeping pattern. Furthermore, the incidence of SCZ has been found to be higher at higher latitudes[60], a pattern that's shared with SAD, and it has been shown that there is a season of birth effect for SCZ[61], and likewise for SAD[62] which has led to the hypothesis that vitamin D plays a crucial role in the etiology of SCZ[63]. Vitamin D improves mood in healthy individuals[48] during winter and reduces depression scores in patients with SAD[49]. The results of this study suggest that in addition to environmental modifiable risk factors such as UVB radiation, photoperiod, visible light intensity, vitamin D supplementation and levels, skin exposure (e.g. sunscreen, reduced outdoor activities), weight increase (resulting in lowering of vitamin D levels[64, 65]), SAD and SCZ share previously unacknowledged genetic risk factors that deserve studies in their own right. However, our study only provides evidence for an overlap in genetic risk factors between SCZ and seasonality. Further evidence for an association between seasonality is needed at both the genetic, environmental and clinical levels before seasonality can be considered as a component of SCZ.

In conclusion, we provide direct evidence for an expected genetic overlap in risk between bipolar disorder (but not major depressive disorder) and seasonality, and an somewhat less expected overlap between schizophrenia and seasonality. Further investigation of the links between bipolar, schizophrenia and SAD at both the clinical and molecular level are warranted and may lead, in the long run, to studies that uncover novel therapeutic targets.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

University of Queensland and Queensland Institute of Medical Research

This research was directly supported by the Australian Research Council (FT0991360) and the Australian National Health and Medical Research Council (613608). EMB is supported by the National Health and Medical Research Early Career Fellowship Scheme. We acknowledge Professor Matthew Brown for Genotyping undertaken at the University of Queensland Centre for Clinical Genomics, housed at UQ's Diamantina Institute. A portion of the statistical analyses were carried out on the GenEpi Cluster, which is financially supported by contributions from grants from the Australian National Health and Medical Research Council (389892; 496682; 496688; 496739; 613672) and ARC (FT0991022; FT0991360). We thank the ATR twins for their continued participation. We also thank Dixie Statham, Bronwyn Morris and Megan Ferguson for coordinating the data collection for the twins; David Smyth, Olivia Zheng and Harry Beeby for data management of the ATR; Anjali Henders, Lisa Bowdler, Steven Crooks (DNA processing); Sarah Medland, Dale Nyholt and Scott Gordon (imputation and genotyping QC). The MARC7 study is supported by NIH grant AA011998 _5978.

The Old Order Amish Study

Supported by 1K18MH093940-01 (PI Postolache). The authors thank the entire research and liason staff of the Amish Research Clinic of the University of Maryland for their overall support, in particular to Nancy Weitzel for her help with the coordination of the study. We also thank Aamar Sleemi, Sarah J. Hinman, Tyler B. Jennings, Hira Mohyuddin, Nadine Postolache, Jayesh K. Hemnani, and Nicholas A. Heroux for help with mailing and scoring the questionnaires, database and bibliographic management. Finally, we very much appreciate the excellent administrative assistance of Christine Ballwanz, Neal Gallico and Francis Iyoriobhe throughout this project.

The Psychiatric Genetics Consortium

The PGC-CDG is supported by NIMH grant U01 MH085520. A portion of the statistical analyses were carried out on the Genetic Cluster Computer (http://www.geneticcluster.org) which is financially supported by the Netherlands Scientific Organization (NWO 480-05-003 PI Posthuma) along with a supplement from the Dutch Brain Foundation and the VU University Amsterdam. Numerous (>100) grants from government agencies along with substantial private and foundation support world-wide enabled the phenotype and genotype data collection without which this research would be not be possible; these grants are listed in the primary PGC publications. We thank the PGC-BPD and PGC SCZ working groups for making available to the research community the genome-wide association results from their published mega-analyses.

Role of the funding source:

The funding agencies had no input in study design; in the collection, analysis, interpretation of data; in the writing of the report or in the decision to submit the paper for publication

REFERENCES

1. Wehr TA, Rosenthal NE. Seasonality and affective illness. The American journal of psychiatry. 1989 Jul; 146(7):829–839. [PubMed: 2662784]
2. Rosenthal NE, Sack DA, Gillin JC, et al. Seasonal affective disorder. A description of the syndrome and preliminary findings with light therapy. Archives of general psychiatry. 1984 Jan; 41(1):72–80. [PubMed: 6581756]
3. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (4th Ed.). 1994
4. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th ed., (DSM-5). Washington DC: American Psychiatric Publishing; 2013.
5. Rosenthal NE. Issues for DSM-V: seasonal affective disorder and seasonality. The American journal of psychiatry. 2009 Aug; 166(8):852–853. [PubMed: 19651748]
6. Wehr TA. Photoperiodism in humans and other primates: evidence and implications. J Biol Rhythms. 2001 Aug; 16(4):348–364. [PubMed: 11506380]
7. Golden RN, Gaynes BN, Ekstrom RD, et al. The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. The American journal of psychiatry. 2005 Apr; 162(4):656–662. [PubMed: 15800134]
8. Terman M, Terman JS, Ross DC. A controlled trial of timed bright light and negative air ionization for treatment of winter depression. Archives of general psychiatry. 1998 Oct; 55(10):875–882. [PubMed: 9783557]
9. Eastman CI, Young MA, Fogg LF, Liu L, Meaden PM. Bright light treatment of winter depression: a placebo-controlled trial. Archives of general psychiatry. 1998 Oct; 55(10):883–889. [PubMed: 9783558]
10. Lewy AJ, Bauer VK, Cutler NL, et al. Morning vs evening light treatment of patients with winter depression. Archives of general psychiatry. 1998 Oct; 55(10):890–896. [PubMed: 9783559]
11. Pendse BP, Engstrom G, Traskman-Bendz L. Psychopathology of seasonal affective disorder patients in comparison with major depression patients who have attempted suicide. The Journal of clinical psychiatry. 2004 Mar; 65(3):322–327. quiz 452–323. [PubMed: 15096070]
12. Sullivan B, Payne TW. Affective disorders and cognitive failures: a comparison of seasonal and nonseasonal depression. The American journal of psychiatry. 2007 Nov; 164(11):1663–1667. [PubMed: 17974930]
13. Kasper S, Wehr TA, Bartko JJ, Gaist PA, Rosenthal NE. Epidemiological findings of seasonal changes in mood and behavior. A telephone survey of Montgomery County, Maryland. Archives of general psychiatry. 1989 Sep; 46(9):823–833. [PubMed: 2789026]

14. Schlager D, Froom J, Jaffe A. Winter depression and functional impairment among ambulatory primary care patients. Comprehensive psychiatry. 1995 Jan-Feb;36(1):18–24. [PubMed: 7705083]
15. Sher L. Genetic studies of seasonal affective disorder and seasonality. Comprehensive psychiatry. 2001 Mar-Apr;42(2):105–110. [PubMed: 11244145]
16. Allen JM, Lam RW, Remick RA, Sadovnick AD. Depressive symptoms and family history in seasonal and nonseasonal mood disorders. The American journal of psychiatry. 1993 Mar; 150(3): 443–448. [PubMed: 8434660]
17. White DM, Lewy AJ, Sack RL, Blood ML, Wesche DL. Is winter depression a bipolar disorder? Comprehensive psychiatry. 1990 May-Jun;31(3):196–204. [PubMed: 2340714]
18. Madden PA, Heath AC, Rosenthal NE, Martin NG. Seasonal changes in mood and behavior. The role of genetic factors. Archives of general psychiatry. 1996 Jan; 53(1):47–55. [PubMed: 8540777]
19. Rosenthal, NEGM.; Sack, DA.; Skwerer, RG.; Wehr, TA. Seasonal affective disorder and its relevance for the understanding and treatment of bulimia. In: Hudson, JIPHJ., editor. The Psychology of Bulimia. Washington D.C.: American Psychiatric Press Inc.; 1987. p. 205-228.
20. Sohn CH, Lam RW. Treatment of seasonal affective disorder: unipolar versus bipolar differences. Curr Psychiatry Rep. 2004 Dec; 6(6):478–485. [PubMed: 15538998]
21. Roecklein KA, Rohan KJ, Postolache TT. Is seasonal affective disorder a bipolar variant? Curr Psychiatr. 2010 Feb; 9(2):42–54. [PubMed: 20495687]
22. Rosenthal NE, Mazzanti CM, Barnett RL, et al. Role of serotonin transporter promoter repeat length polymorphism (5-HTTLPR) in seasonality and seasonal affective disorder. Molecular psychiatry. 1998 Mar; 3(2):175–177. [PubMed: 9577843]
23. Sher L, Goldman D, Ozaki N, Rosenthal NE. The role of genetic factors in the etiology of seasonal affective disorder and seasonality. Journal of affective disorders. 1999 Jun; 53(3):203–210. [PubMed: 10404705]
24. Molnar E, Lazary J, Benko A, et al. Seasonality and winter-type seasonal depression are associated with the rs731779 polymorphism of the serotonin-2A receptor gene. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology. 2010 Sep; 20(9):655–662. [PubMed: 20580209]
25. Lenzinger E, Neumeister A, Praschak-Rieder N, et al. Behavioral effects of tryptophan depletion in seasonal affective disorder associated with the serotonin transporter gene? Psychiatry research. 1999 Mar 22; 85(3):241–246. [PubMed: 10333377]
26. Willeit M, Praschak-Rieder N, Neumeister A, et al. A polymorphism (5-HTTLPR) in the serotonin transporter promoter gene is associated with DSM-IV depression subtypes in seasonal affective disorder. Molecular psychiatry. 2003 Nov; 8(11):942–946. [PubMed: 14593433]
27. Roecklein KA, Rohan KJ, Duncan WC, et al. A missense variant (P10L) of the melanopsin (OPN4) gene in seasonal affective disorder. Journal of affective disorders. 2009 Apr; 114(1–3): 279–285. [PubMed: 18804284]
28. Ripke S, Sanders AR, Kendler KS, et al. Genome-wide association study identifies five new schizophrenia loci. Nature genetics. 2011 Oct; 43(10):969–976. [PubMed: 21926974]
29. Ripke S, O'Dushlaine C, Chambert K, et al. Genome-wide association analysis identifies 13 new risk loci for schizophrenia. Nature genetics. 2013 Oct; 45(10):1150–1159. [PubMed: 23974872]
30. Sklar P, Ripke S, Scott LJ, et al. Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. Nature genetics. 2011 Oct; 43(10):977–983. [PubMed: 21926972]
31. Lee SH, Ripke S, et al. Cross-Disorder Group of the Psychiatric Genomics C. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. Nature genetics. 2013 Sep; 45(9):984–994. [PubMed: 23933821]
32. Rosenthal, NE.; Genhart, MJ.; Sack, DA.; Skwerer, RG.; Wehr, TA. Seasonal affective disorder and its relevance for the understanding and treatment of bulimia. In: Hudson, JI.; Pope, HG., Jr, editors. The Psychology of Bulimia. Washington, D.C.: American Psychiatric Press Inc; 1987. p. 205-228.
33. Hsueh WC, Silver KD, Pollin TI, et al. A genome-wide linkage scan of insulin level derived traits: the Amish Family Diabetes Study. Diabetes. 2007 Oct; 56(10):2643–2648. [PubMed: 17646211]

34. Mitchell BD, McArdle PF, Shen H, et al. The genetic response to short-term interventions affecting cardiovascular function: rationale and design of the Heredity and Phenotype Intervention (HAPI) Heart Study. Am Heart J. 2008 May; 155(5):823–828. [PubMed: 18440328]
35. Rampersaud E, Mitchell BD, Pollin TI, et al. Physical activity and the association of common FTO gene variants with body mass index and obesity. Arch Intern Med. 2008 Sep 8; 168(16):1791–1797. [PubMed: 18779467]
36. Streeten EA, McBride DJ, Pollin TI, et al. Quantitative trait loci for BMD identified by autosome-wide linkage scan to chromosomes 7q and 21q in men from the Amish Family Osteoporosis Study. J Bone Miner Res. 2006 Sep; 21(9):1433–1442. [PubMed: 16939402]
37. Kuehner RM, Vaswani D, Raheja UK, et al. Test-retest reliability of the Seasonal Pattern Assessment Questionnaire in Old Order Amish. International journal on disability and human development : IJDHD. 2013 Feb; 12(1):87–90. [PubMed: 23565353]
38. Raheja UK, Stephens SH, Mitchell BD, et al. Seasonality of mood and behavior in the Old Order Amish. Journal of affective disorders. 2013 May; 147(1–3):112–117. [PubMed: 23164460]
39. Li Y, Willer CJ, Ding J, Scheet P, Abecasis GR. MaCH: using sequence and genotype data to estimate haplotypes and unobserved genotypes. Genetic epidemiology. 2010 Dec; 34(8):816–834. [PubMed: 21058334]
40. Abecasis GR, Cherny SS, Cookson WO, Cardon LR. Merlin--rapid analysis of dense genetic maps using sparse gene flow trees. Nature genetics. 2002 Jan; 30(1):97–101. [PubMed: 11731797]
41. Chen WM, Abecasis GR. Family-based association tests for genomewide association scans. American journal of human genetics. 2007 Nov; 81(5):913–926. [PubMed: 17924335]
42. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. Bioinformatics. 2010 Sep 1; 26(17):2190–2191. [PubMed: 20616382]
43. Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium. A mega-analysis of genome-wide association studies for major depressive disorder. Molecular psychiatry. 2012 Apr 3.
44. Purcell SM, Wray NR, Stone JL, et al. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature. 2009 Aug 6; 460(7256):748–752. [PubMed: 19571811]
45. Ferreira MA, O'Donovan MC, Meng YA, et al. Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder. Nature genetics. 2008 Sep; 40(9): 1056–1058. [PubMed: 18711365]
46. Sklar P, Smoller JW, Fan J, et al. Whole-genome association study of bipolar disorder. Molecular psychiatry. 2008 Jun; 13(6):558–569. [PubMed: 18317468]
47. Wray NR, Pergadia ML, Blackwood DH, et al. Genome-wide association study of major depressive disorder: new results, meta-analysis, and lessons learned. Molecular psychiatry. 2012 Jan; 17(1):36–48. [PubMed: 21042317]
48. Doorack JE, Allen J, Battaglia J. Co-occurring SAD symptomatology and schizophrenia at high latitude: a pilot study. Int J Circumpolar Health. 2007 Jun; 66(3):248–256. [PubMed: 17655065]
49. Strous RD, Pollack S, Robinson D, Sheitman B, Lieberman JA. Seasonal admission patterns in first episode psychosis, chronic schizophrenia, and nonschizophrenic psychoses. The Journal of nervous and mental disease. 2001 Sep; 189(9):642–644. [PubMed: 11580010]
50. Faust V, Sarreither P. Season and psychiatric disease (author's transl). Medizinische Klinik. 1975 Mar 14; 70(11):467–473. [PubMed: 1091831]
51. Hare EH, Walter SD. Seasonal variation in admissions of psychiatric patients and its relation to seasonal variation in their births. Journal of epidemiology and community health. 1978 Mar; 32(1):47–52. [PubMed: 262589]
52. Takei N, Murray RM. Gender difference of schizophrenia in seasonal admissions in Scotland. The British journal of psychiatry : the journal of mental science. 1993 Feb.162:272–273. [PubMed: 8435709]
53. Clarke M, Moran P, Keogh F, et al. Seasonal influences on admissions in schizophrenia and affective disorder in Ireland. Schizophrenia research. 1998 Nov 30; 34(3):143–149. [PubMed: 9850980]

54. Clarke M, Moran P, Keogh F, et al. Seasonal influences on admissions for affective disorder and schizophrenia in Ireland: a comparison of first and readmissions. European psychiatry : the journal of the Association of European Psychiatrists. 1999 Sep; 14(5):251–255. [PubMed: 10572354]
55. Shiloh R, Shapira A, Potchter O, Hermesh H, Popper M, Weizman A. Effects of climate on admission rates of schizophrenia patients to psychiatric hospitals. European psychiatry : the journal of the Association of European Psychiatrists. 2005 Jan; 20(1):61–64. [PubMed: 15642446]
56. Amr M, Volpe FM. Seasonal influences on admissions for mood disorders and schizophrenia in a teaching psychiatric hospital in Egypt. Journal of affective disorders. 2012 Mar; 137(1–3):56–60. [PubMed: 22244374]
57. Davies G, Ahmad F, Chant D, Welham J, McGrath J. Seasonality of first admissions for schizophrenia in the Southern Hemisphere. Schizophrenia research. 2000 Feb 14; 41(3):457–462. [PubMed: 10728722]
58. Owens N, McGorry PD. Seasonality of symptom onset in first-episode schizophrenia. Psychological medicine. 2003 Jan; 33(1):163–167. [PubMed: 12537047]
59. Daniels BA, Kirkby KC, Mitchell P, Hay D, Mowry B. Seasonal variation in hospital admission for bipolar disorder, depression and schizophrenia in Tasmania. Acta psychiatrica Scandinavica. 2000 Jul; 102(1):38–43. [PubMed: 10892608]
60. Saha S, Chant DC, Welham JL, McGrath JJ. The incidence and prevalence of schizophrenia varies with latitude. Acta psychiatrica Scandinavica. 2006 Jul; 114(1):36–39. [PubMed: 16774659]
61. Torrey EF, Miller J, Rawlings R, Yolken RH. Seasonality of births in schizophrenia and bipolar disorder: a review of the literature. Schizophrenia research. 1997 Nov 7; 28(1):1–38. [PubMed: 9428062]
62. Pjrek E, Winkler D, Heiden A, et al. Seasonality of birth in seasonal affective disorder. The Journal of clinical psychiatry. 2004 Oct; 65(10):1389–1393. [PubMed: 15491243]
63. McGrath J. Hypothesis: is low prenatal vitamin D a risk-modifying factor for schizophrenia? Schizophrenia research. 1999 Dec 21; 40(3):173–177. [PubMed: 10638855]
64. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. The American journal of clinical nutrition. 2000 Sep; 72(3):690–693. [PubMed: 10966885]
65. Vimaleswaran KS, Berry DJ, Lu C, et al. Causal relationship between obesity and vitamin D status: bi-directional Mendelian randomization analysis of multiple cohorts. PLoS medicine. 2013; 10(2):e1001383. [PubMed: 23393431]

CLINICAL POINTS

- Our study provides evidence for an expected overlap between seasonality of mood and bipolar disorder and a somewhat unexpected genetic overlap seasonality of mood and schizophrenia. There was no genetic overlap between major depression and seasonality.
- If replicated, our results would imply that seasonal changes in mood and behavior should be evaluated not only in individuals diagnosed with mood disorders, but also in patients with schizophrenia. Clinical symptoms that overlap between seasonal affective disorder and schizophrenia include cognitive impairment, social withdrawal, and sleep changes, and both conditions share associations with certain metabolic abnormalities, such as Vitamin D deficiency.
- Future research may specifically focus on molecular pathways mediating the overlap between seasonality and schizophrenia and bipolar disorder, potentially leading to theoretical advances and novel therapeutic interventions.

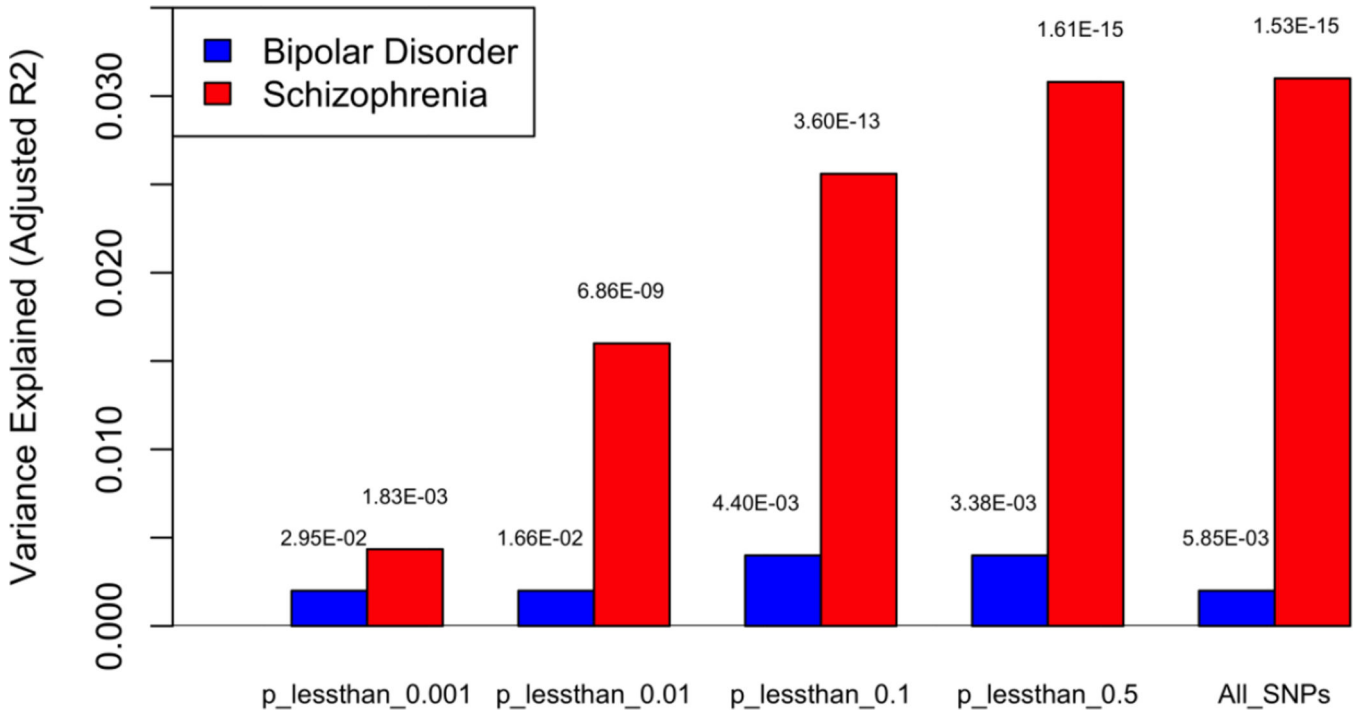

Figure 1.

Results from profile scoring analyses using PGC schizophrenia and bipolar GWAS results. The variance explained in seasonality by the profile scores is shown on the Y-axis. The significance for each analysis is listed on the top of each bar.

Table 1

Descriptive Statistics for the Australian and Amish cohorts

Australian sample	n = 3269
Mean Age (Range)	35.7 ± 13.3 (19– 78)
% male	34.8
Mean GSS	5.6 ± 3.9
Old Order Amish	n = 887
Mean age	55.9 ± 15.2
% men	47.5
Mean GSS	4.5 ± 3.4