See commentary by Goes and DePaulo p152

Seasonality Shows Evidence for Polygenic Architecture and Genetic Correlation With Schizophrenia and Bipolar Disorder

Enda M. Byrne, PhD, for the Psychiatric Genetics Consortium Major Depressive Disorder Working Group; Uttam K. Raheja, MD; Sarah H. Stephens, PhD; Andrew C. Heath, DPhil; Pamela A. F. Madden PhD; Dipika Vaswani, MD; Gagan V. Nijjar, MD; Kathleen A. Ryan, MS; Hassaan Youssufi, BS; Philip R. Gehrman, PhD; Alan R. Shuldiner, MD; Nicholas G. Martin, PhD; Grant W. Montgomery, PhD; Naomi R. Wray, PhD; Elliot C. Nelson, MD; Braxton D. Mitchell, PhD; and Teodor T. Postolache, MD

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.

Method: Genome-wide association studies (GWASs) were conducted in Australian (between 1988 and 1990 and between 2010 and 2013) and Amish (between May 2010 and December 2011) samples in whom the Seasonal Pattern Assessment Questionnaire (SPAQ) had been administered, and the results were meta-analyzed in a total sample of 4,156 individuals. Genetic risk scores based on results from prior large GWAS studies of bipolar disorder, major depressive disorder (MDD), and schizophrenia were calculated to test for overlap in risk between psychiatric disorders and seasonality.

Results: The most significant association was with rs11825064 ($P = 1.7 \times 10^{-6}$, $\beta = 0.64$, standard error = 0.13), an intergenic single nucleotide polymorphism (SNP) found on chromosome 11. The evidence for overlap in risk factors was strongest for schizophrenia and seasonality, with the schizophrenia genetic profile scores explaining 3% of the variance in log-transformed global seasonality scores. Bipolar disorder genetic profile scores were also associated with seasonality, although at much weaker levels (minimum P value $= 3.4 \times 10^{-3}$), and no evidence for overlap in risk was detected between MDD and seasonality.

Conclusions: Common SNPs of large effect most likely do not exist for seasonality in the populations examined. As expected, there were overlapping genetic risk factors for bipolar disorder (but not MDD) with seasonality. Unexpectedly, the risk for schizophrenia 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 schizophrenia.

J Clin Psychiatry 2015;76(2):128–134

Submitted: *January 2, 2014; accepted August 29, 2014.*
Online ahead of print: *December 9, 2014 (doi:10.4088/JCP.14m08981).*
Corresponding author: *Enda M. Byrne, PhD, The University of Queensland, Queensland Brain Institute, Upland Rd, St Lucia, QLD 4072, Brisbane, Australia (enda.byrne@uq.edu.au).*

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 2 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] has argued from many lines of evidence that SAD should be considered an independent clinical entity rather than a seasonal mood specifier. Seasonal affective disorder 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] Symptoms of SAD are particularly responsive to bright light treatment.[7–10] Contrary to common expectations, patients with SAD can manifest severe symptomatology[11,12] and cognitive deficits[12] similar to nonseasonal depression.[12] Seasonal affective disorder 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 patients with SAD.[16,17] A previous analysis of a large epidemiologic 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 individuals with SAD, but the question of whether seasonality and depression are distinct in terms of the genetic risk factors that predispose to them remains unanswered.[15]

Table 1. Descriptive Statistics for the Australian and Amish Cohorts

Cohort	Value
Australian sample	
n	3,269
Age, mean ± SD (range), y	35.7 ± 13.3 (19–78)
Men, %	34.8
Global seasonality score, mean ± SD	5.6 ± 3.9
Old Order Amish	
n	887
Age, mean ± SD (range), y	55.9 ± 15.2 (21–99)
Men, %	47.5
Global seasonality score, mean ± SD	4.5 ± 3.4

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 (GWASs) have been successful in mapping genetic variants that increase risk of schizophrenia[28,29] and BD[30]; however, large sample sizes have been required to detect them. No GWASs 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 3 psychiatric disorders—major depressive disorder (MDD), BD, and schizophrenia.

METHOD

Seasonal Pattern Assessment Questionnaire

A well-studied SAD screening and research questionnaire, the SPAQ[32] evaluates SAD by estimating a score of global seasonality calculated by responses on a Likert scale of 0–4 for each of 6 indices of seasonality, the degree to which these changes cause impaired functioning (the problem scale, ranging from 0 to 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 global seasonality indices, the global seasonality score was estimated from the proportion of responses.

Australian Samples

Participants were drawn from 2 studies conducted between 1988 and 1990 and between 2010 and 2013 at the Queensland Institute of Medical Research. The first study, which has been 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 second study, the Midwest Alcohol Research Center study, is a collaborative study between investigators at Queensland Institute of Medical Research and Washington University in St Louis, Missouri, 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[33]). Participants undertook 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 Queensland Institute of Medical Research. 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 global seasonality scores after adjusting for these effects were tested for association. Global seasonality scores from all phenotyped individuals were used to extract the residuals.

Clinical Points

- Our study provides evidence for an expected overlap between seasonality of mood and bipolar disorder and a somewhat unexpected genetic overlap between 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.

Genotyping. Full details of the genotyping, imputation, and quality control procedures are given in the supplementary material. After genotyping, quality control, and imputation, a total number of 2,380,486 single nucleotide polymorphisms (SNPs) were included.

Amish

Participants in the study were Amish individuals enrolled in community-based studies[34–37] conducted between May 2010 and December 2011 at the University of Maryland and University of Maryland's Amish Research Clinic in Lancaster County, Pennsylvania. The participants consented to be contacted for future studies. Seasonal Pattern Assessment Questionnaires 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 in September 2010 was done for those who had not responded to the initial mailing. 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 global seasonality and problem rating score (PRS) in the Amish was adequate using Cronbach α (global seasonality, $\alpha = .87$; PRS, $\alpha = .79$)[38] and comparable to that in the general population.[39]

Genotyping. Genotyping was performed using the Affymetrix GeneChip Human Mapping 500 K or 6.0 Array set (Affymetrix, Santa Clara, California). Genotype calls were made using the Bayesian robust linear model with mahalanobis distance classifier genotype calling algorithm. A total of 364,336 informative autosomal SNPs that passed quality control were included in the analysis. Markov Chain Haplotyping (MaCH)[40] was used for imputation (release 22, build 36) after applying the following exclusion filters: (1) SNP not found in HapMap; (2) frequency < 0.01; (3) Hardy-Weinberg P value $< 1 \times 10^{-6}$; and (4) missingness > 0.05.

Association Analysis

Association testing in the Australian sample was performed in Merlin,[41,42] 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), which accounts for family structure by conditioning the association of genotype with outcome on the relationship matrix (included as a random effect) and covariates (eg, age and sex). Meta-analysis was performed using the inverse variance weighting method in METAL.[43]

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 minor allele frequency of 0.2 that explains 1% of the phenotypic variance in global seasonality. The Australian sample had 50.8% power to detect such a variant at the genome-wide significance threshold. The sample had 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 global seasonality, and mood disorders, utilizing the results from the Psychiatric GWAS Consortium (PGC) GWAS analyses of schizophrenia,[28] BD,[30] and MDD[44] 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, 3 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 by Purcell et al[45] and used to demonstrate that there is overlap in the genetic risk factors for schizophrenia and BD.

We used the summary results from the PGC BD and schizophrenia GWAS analyses separately (downloaded from http://www.med.unc.edu/pgc). The schizophrenia study included 9,394 cases and 12,462 controls, and the BP 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 linkage disequilibrium block is included in the analysis and that the same association signal is not included more than once. We also generated profile scores using association results from PGC MDD.[44] However, since samples from the Queensland Institute of Medical Research contribute to PGC MDD analysis, the PGC MDD data were reanalyzed with the Australian samples excluded, so as to remove any chance of overlap between the discovery and target samples. A total of 7,790 cases and 7,808 controls were included in the revised PGC MDD analysis. The results from this GWAS analysis were used in the MDD profile score analysis.

RESULTS

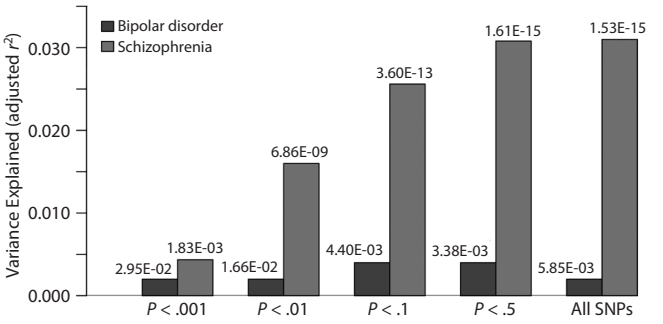
Genome-Wide Association Study

Results from the most significantly associated SNPs ($P < 10^{-5}$) from the Australian sample are shown in

Supplementary eTable 1. No SNPs reached genome-wide significance in the initial GWAS. All SNPs that had a P value $< 10^{-4}$ and that were independent at $r^2 < 0.5$ or > 50 kilobase (kb) away from each other 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 ($P < .05$).

A total of 2,354,422 markers that were in common between the 2 studies were included in a meta-analysis of the 2 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 ($P = 1.7 \times 10^{-6}$, $\beta = 0.64$, standard error [SE] = 0.13), an intergenic SNP found on chromosome 11. A list of the most significant results is provided in Supplementary eTable 2. A description of the GWAS results and meta-analysis in addition to results from analyses to estimate the heritability explained by all SNPs is reported in Supplementary Methods. 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.

Figure 1. Results From Profile Scoring of Seasonality Using PGC GWAS Results in Australian Sample[a]



[a]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.

Abbreviations: GWAS = genome-wide association study, PGC = Psychiatric GWAS Consortium, SNP = single nucleotide polymorphism.

Genetic Overlap Using Profile Scoring

The results for the profile score analysis for all 3 disorders are shown in Supplementary eTable 3. The results for BD and schizophrenia are also shown in Figure 1. There is very strong evidence for genetic overlap between schizophrenia and seasonality ($P < 1 \times 10^{-15}$ for genetic scores based on SNPs associated with schizophrenia at $P < .5$ or all SNPs) and milder evidence for genetic overlap between BD and seasonality ($P = .004$–$.005$ for genetic scores based on SNPs associated with schizophrenia at $P < .1$, $P < .5$, or all SNPs). The genetic risk score for schizophrenia accounted for up to 3.1% of the phenotypic variation in global seasonality. A nominally significant proportion of the variance in the global seasonality was explained by 427 SNPs, with $P < .001$ from the PGC schizophrenia GWAS ($P = .0018$, variance explained = 0.4%). The null hypothesis that the variance explained by all the schizophrenia SNPs is 0 was rejected ($P = 1.53 \times 10^{-15}$). In contrast, genetic risk score for BD accounted for only 0.4% of the phenotypic variation in global seasonality (see Supplementary eTable 4). No evidence for genetic overlap between MDD and seasonality was observed, as the amount of variance in global seasonality explained by the MDD polygenic scores was not significantly different from 0.

DISCUSSION

We performed a meta-analysis of 2 GWASs of the global seasonality 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 significant proportion of the heritability of affected disorders.[28,45–47] Our results suggest that common variants that are associated with seasonality and that have unusually large effect 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 they provide a list of candidates that can be tested in other cohorts.

The differences between the 2 populations included in this study may have also increased the chances of negative findings. The geographical differences between Australia and the Northeast 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,[39] a somewhat lower estimate than that 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 white 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. Among Anabaptists there is a low rate of psychosis.[48,49]

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 schizophrenia 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 schizophrenia. The finding that the schizophrenia profile scores explain a larger proportion of variance in the global seasonality may be due to differences between the GWASs 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 schizophrenia 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 global seasonality 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 for this is that the estimates of the SNP effects from the MDD GWAS may be less accurate than those from the schizophrenia and BD GWASs. It has been argued that a GWAS of MDD has less power than a GWAS of schizophrenia or BD of the same sample size, simply reflecting that MDD is a more prevalent disorder, is potentially more heterogeneous, and has a lower proportion of risk explained by genetic factors.[50]

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[1]). To our knowledge, our current report provides the first direct evidence at the molecular level for the overlap between seasonality and BD that has been previously suggested clinically.[21]

While the association between seasonality of mood and schizophrenia was unexpected, a hint of a relationship was reported in small samples at high latitudes.[51] Specifically, Doorack et al[51] examined SAD symptoms in patients with schizophrenia in Alaska and found that 36% had co-occurring SAD. Moreover, previous studies have suggested an association between onset of the first episode of schizophrenia and season (eg, Strous et al[52]). Additionally, studies conducted in the northern hemisphere found a summer peak of schizophrenia admissions in hospitals.[53–55] In England and Wales, for example, Hare and Walter[54] found a summer peak of schizophrenia admissions. Clarke et al[56] 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[57] found that the seasonal association held only for first admissions and not for subsequent admissions. Shiloh et al[58] found a summer peak for schizophrenia admissions in Israel. In China, Tian et al[59] 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,[57] may be necessary to isolate seasonality effects. However, there are studies that found no seasonal variation in schizophrenia or that found patterns contrary to those previously reported. For example, Aviv et al[60] as well as Amr and Volpe[61] did not find any seasonal effect on admission rates. In the southern hemisphere, Davies et al[62] found a peak in first-episode schizophrenia admission in the winter (August), similar to Owens and McGorry.[63] In contrast, Daniels et al[64] did not find a seasonal association in admissions with diagnoses of schizophrenia and bipolar disorder in Tasmania.

There are certain clinical symptoms that overlap between SAD and schizophrenia, including cognitive deficits, social withdrawal, and changes in sleeping pattern. Furthermore, the incidence of schizophrenia has been found to be higher at higher latitudes,[65] a pattern that is shared with SAD, and it has been shown that there is a season of birth effect for schizophrenia,[66] and likewise for SAD,[67] which has led to the hypothesis that vitamin D plays a crucial role in the etiology of schizophrenia.[68] Vitamin D improves mood in healthy individuals[51] during winter and reduces depression scores in patients with SAD.[52] The results of this study suggest that, in addition to environmental modifiable risk factors such as ultraviolet B radiation, photoperiod, visible light intensity, vitamin D supplementation and levels, skin exposure (eg, sunscreen, reduced outdoor activities), and weight increase (resulting in lowering of vitamin D levels[69,70]), SAD and schizophrenia share previously unacknowledged genetic risk factors that deserve studies in their own right. However, our study provides evidence only for an overlap in genetic risk factors between schizophrenia and seasonality. Further evidence for an association between seasonality and schizophrenia is needed at the genetic, environmental, and clinical levels before seasonality can be considered as a component of schizophrenia.

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

Author affiliations: The University of Queensland, Queensland Brain Institute, St. Lucia (Drs Byrne and Wray); Queensland Institute of Medical Research, Herston (Drs Byrne, Martin, and Montgomery), Australia; Mood and Anxiety Program, Department of Psychiatry (Drs Raheja, Vaswani, Nijjar, and Postolache and Mr Youssufi); Division of Endocrinology, Diabetes and Nutrition, Department of Medicine (Drs Stephens, Shuldiner, and Mitchell and Ms Ryan); and Division of Child and Adolescent Psychiatry & University of Maryland Child and Adolescent Mental Health Innovations Center (Dr Postolache), University of Maryland School of Medicine; Geriatric Research and Education Clinical Center, Veterans Administration Medical Center, (Drs Shuldiner and Mitchell), Baltimore, Maryland; Saint Elizabeths Hospital, Psychiatry Residency Training Program (Drs Raheja and Postolache); National Center for the Treatment of Phobias, Anxiety and Depression (Dr Postolache), Washington, DC; Department of Psychiatry, Washington University, St Louis, Missouri (Drs Heath, Madden, and Nelson); Department of Psychiatry, Kaiser Permanente, Santa Rosa California (Dr Nijjar); and Behavioral Sleep Medicine Program, Department of Psychiatry and Penn Sleep Center, University of Pennsylvania, Philadelphia (Dr Gehrman).
Potential conflicts of interest: None reported.
Funding/support: 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). Dr Byrne is supported by the Australian National Health and Medical Research Early Career Fellowship Scheme. A portion of the statistical analyses was 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 Australian Research Council (FT0991022, FT0991360). The Midwest Alcohol Research Center study is supported by US National Institutes of Health (NIH) grant AA011998 _5978.
Old Order Amish Study: Supported by NIH grant 1K18MH093940-01 (principal investigator: Dr Postolache). Partial funding was also provided by the Mid-Atlantic Nutrition and Obesity Research Center (P30 DK072488).
The Psychiatric Genetics Consortium: The PGC–Cross-Disorder Group is supported by US National Institute of Mental Health 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 (Netherlands Organization for Science Research 480-05-003; principal investigator: D. Posthuma, PhD) 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 worldwide 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.
Role of the sponsors: 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.
Acknowledgments: University of Queensland and Queensland Institute of Medical Research: The authors acknowledge Matthew Brown, MD, for genotyping undertaken at the University of Queensland Centre for Clinical Genomics, housed at University of Queensland's Diamantina Institute. The authors thank the Australian Twin Registry (ATR) twins for their continued participation. The authors also thank Dixie Statham, MPsych; Bronwyn Morris, BSc; and Megan Ferguson, BSc, for coordinating the data collection for the twins; David Smyth, BSc; Olivia Zheng, BSc; and Harry Beeby, BSc, for data management of the ATR; Anjali Henders, BSc; Lisa Bowdler, BSc; and Steven Crooks, BSc (DNA processing); Sarah Medland, PhD; Dale Nyholt, PhD; and Scott Gordon, PhD (imputation and genotyping quality control). These individuals are affiliated with The Queensland Institute of Medical Research and have no conflict of interest to declare.
The Old Order Amish Study: The authors thank the entire research and liason staff of the Amish Research Clinic, University of Maryland for their overall support, in particular to Nancy Weitzel, RN, for her help with the coordination of the study. The authors also thank Aamar Sleemi, MD; Sarah J. Hinman, BSc; Tyler B. Jennings, BSc; Hira Mohyuddi, BSc; Nadine Postolache, BSc; Jayesh K. Hemnani, BSc; and Nicholas A. Heroux, BSc, from Amish Research Clinic, University of Maryland, for help with mailing and scoring the questionnaires and database and bibliographic management. The authors appreciate Christine Eder; Neal Gallico, MS; and Francis Iyoriobhe, MBA, CPA, from the University of Maryland, for their excellent administrative assistance throughout this project. These individuals have no conflicts of interest to report.
The Psychiatric Genetics Consortium: The authors thank the PGC-Bipolar Disorder and PGC-Schizophrenia working groups for making available to the research community the genome-wide association results from their published mega-analyses. Information on PGC and obtaining access to genotype data can be found at www.med.unc.edu/pgc. Psychiatric GWAS Consortium (PGC) contributors and affiliations are listed in Supplementary eTable 4.
Supplementary material: Available at PSYCHIATRIST.COM.

REFERENCES

1. Wehr TA, Rosenthal NE. Seasonality and affective illness. *Am J Psychiatry*. 1989;146(7):829–839.
2. Rosenthal NE, Sack DA, Gillin JC, et al. Seasonal affective disorder: a description of the syndrome and preliminary findings with light therapy. *Arch Gen Psychiatry*. 1984;41(1):72–80.
3. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition. Washington, DC: American Psychiatric Publishing; 1994.
4. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition. Washington DC: American Psychiatric Publishing; 2013.
5. Rosenthal NE. Issues for *DSM-V*: seasonal affective disorder and seasonality. *Am J Psychiatry*. 2009;166(8):852–853.
6. Wehr TA. Photoperiodism in humans and other primates: evidence and implications. *J Biol Rhythms*. 2001;16(4):348–364.
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. *Am J Psychiatry*. 2005;162(4):656–662.
8. Terman M, Terman JS, Ross DC. A controlled trial of timed bright light and negative air ionization for treatment of winter depression. *Arch Gen Psychiatry*. 1998;55(10):875–882.
9. Eastman CI, Young MA, Fogg LF, et al. Bright light treatment of winter depression: a placebo-controlled trial. *Arch Gen Psychiatry*. 1998;55(10):883–889.
10. Lewy AJ, Bauer VK, Cutler NL, et al. Morning vs evening light treatment of patients with winter depression. *Arch Gen Psychiatry*. 1998;55(10):890–896.
11. Pendse BP, Engström G, Träskman-Bendz L. Psychopathology of seasonal affective disorder patients in comparison with major depression patients who have attempted suicide. *J Clin Psychiatry*. 2004;65(3):322–327, quiz 452–453.
12. Sullivan B, Payne TW. Affective disorders and cognitive failures: a comparison of seasonal and nonseasonal depression. *Am J Psychiatry*. 2007;164(11):1663–1667.
13. Kasper S, Wehr TA, Bartko JJ, et al. Epidemiological findings of seasonal changes in mood and behavior: a telephone survey of Montgomery County, Maryland. *Arch Gen Psychiatry*. 1989;46(9):823–833.
14. Schlager D, Froom J, Jaffe A. Winter depression and functional impairment among ambulatory primary care patients. *Compr Psychiatry*. 1995;36(1):18–24.
15. Sher L. Genetic studies of seasonal affective disorder and seasonality. *Compr Psychiatry*. 2001;42(2):105–110.
16. Allen JM, Lam RW, Remick RA, et al. Depressive symptoms and family history in seasonal and nonseasonal mood disorders. *Am J Psychiatry*. 1993;150(3):443–448.
17. White DM, Lewy AJ, Sack RL, et al. Is winter depression a bipolar disorder? *Compr Psychiatry*. 1990;31(3):196–204.
18. Madden PA, Heath AC, Rosenthal NE, et al. Seasonal changes in mood and behavior; the role of genetic factors. *Arch Gen Psychiatry*. 1996;53(1):47–55.
19. Rosenthal NEGM, Sack DA, Skwerer RG, et al. Seasonal affective disorder and its relevance for the understanding and treatment of bulimia. In: Hudson JIPHJ, ed. *The Psychology of Bulimia*. Washington, DC: American Psychiatric Press, Inc; 1987:205–228.
20. Sohn CH, Lam RW. Treatment of seasonal affective disorder: unipolar versus bipolar differences. *Curr Psychiatry Rep*. 2004;6(6):478–485.
21. Roecklein KA, Rohan KJ, Postolache TT. Is seasonal affective disorder a bipolar variant? *Curr Psychiatr*. 2010;9(2):42–54.
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. *Mol Psychiatry*. 1998;3(2):175–177.
23. Sher L, Goldman D, Ozaki N, et al. The role of genetic factors in the etiology of seasonal affective disorder and seasonality. *J Affect Disord*. 1999;53(3):203–210.
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. *Eur Neuropsychopharmacol*. 2010;20(9):655–662.
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 Res*. 1999;85(3):241–246.
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. *Mol Psychiatry*. 2003;8(11):942–946.
27. Roecklein KA, Rohan KJ, Duncan WC, et al. A missense variant (P10L) of the melanopsin (OPN4) gene in seasonal affective disorder. *J Affect Disord*. 2009;114(1–3):279–285.
28. Ripke S, Sanders AR, Kendler KS, et al; Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium. Genome-wide association study identifies five new schizophrenia loci. *Nat Genet*. 2011;43(10):969–976.
29. Ripke S, O'Dushlaine C, Chambert K, et al; Wellcome Trust Case Control Consortium 2. Genome-wide association analysis identifies 13 new risk loci for schizophrenia. *Nat Genet*. 2013;45(10):1150–1159.
30. Sklar P, Ripke S, Scott LJ, et al; Psychiatric GWAS Consortium Bipolar Disorder Working Group. Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. *Nat Genet*. 2011;43(10):977–983.
31. Lee SH, Ripke S, Neale BM, et al; International Inflammatory Bowel Disease Genetics Consortium (IIBDGC). Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat Genet*. 2013;45(9):984–994.
32. Rosenthal NE, Genhart MJ, Sack DA, et al. Seasonal affective disorder and its relevance for the understanding and treatment of bulimia. In: Hudson JI, Pope HG Jr, eds. *The Psychology of Bulimia*. Washington, DC: American Psychiatric Press Inc; 1987:205–228.
33. Heath AC, Whitfield JB, Martin NG, et al. A quantitative-trait genome-wide association study of alcoholism risk in the community: findings and implications. *Biol Psychiatry.* 2011;70(6):513–518.
34. 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;56(10):2643–2648.
35. 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;155(5):823–828.
36. 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;168(16):1791–1797.
37. 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;21(9):1433–1442.
38. Kuehner RM, Vaswani D, Raheja UK, et al. Test-retest reliability of the Seasonal Pattern Assessment Questionnaire in Old Order Amish. *Int J Disabil Hum Dev*. 2013;12(1):87–90.
39. Raheja UK, Stephens SH, Mitchell BD, et al. Seasonality of mood and behavior in the Old Order Amish. *J Affect Disord*. 2013;147(1–3):112–117.
40. Li Y, Willer CJ, Ding J, et al. MaCH: using sequence and genotype data to estimate haplotypes and unobserved genotypes. *Genet Epidemiol*. 2010;34(8):816–834.
41. Abecasis GR, Cherny SS, Cookson WO, et al. Merlin—rapid analysis of dense genetic maps using sparse gene flow trees. *Nat Genet*. 2002;30(1):97–101.
42. Chen WM, Abecasis GR. Family-based association tests for genomewide association scans. *Am J Hum Genet*. 2007;81(5):913–926.
43. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics*. 2010;26(17):2190–2191.
44. Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium. A mega-analysis of genome-wide association studies for major depressive disorder. *Mol Psychiatry*. 2013;18(4):497–511.
45. Purcell SM, Wray NR, Stone JL, et al; International Schizophrenia Consortium. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature*. 2009;460(7256):748–752.
46. Ferreira MA, O'Donovan MC, Meng YA, et al; Wellcome Trust Case Control Consortium. Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder. *Nat Genet*. 2008;40(9):1056–1058.
47. Sklar P, Smoller JW, Fan J, et al. Whole-genome association study of bipolar disorder. *Mol Psychiatry*. 2008;13(6):558–569.
48. Nimgaonkar VL, Fujiwara TM, Dutta M, et al. Low prevalence of psychoses among the Hutterites, an isolated religious community. *Am J Psychiatry.* 2000;157(7):1065–1070.
49. Torrey EF. Prevalence of psychosis among the Hutterites: a reanalysis of the 1950-53 study. *Schizophr Res.* 1995;16(2):167–170.
50. Wray NR, Pergadia ML, Blackwood DH, et al. Genome-wide association study of major depressive disorder: new results, meta-analysis, and lessons learned. *Mol Psychiatry*. 2012;17(1):36–48.
51. Doorack JE, Allen J, Battaglia J. Co-occurring SAD symptomatology and schizophrenia at high latitude: a pilot study. *Int J Circumpolar Health*. 2007;66(3):248–256.
52. Strous RD, Pollack S, Robinson D, et al. Seasonal admission patterns in first episode psychosis, chronic schizophrenia, and nonschizophrenic psychoses. *J Nerv Ment Dis*. 2001;189(9):642–644.
53. Faust V, Sarreither P. Season and psychiatric disease (author's transl)[in German]. *Med Klin*. 1975;70(11):467–473.
54. Hare EH, Walter SD. Seasonal variation in admissions of psychiatric patients and its relation to seasonal variation in their births. *J Epidemiol Community Health*. 1978;32(1):47–52.
55. Takei N, Murray RM. Gender difference of schizophrenia in seasonal admissions in Scotland. *Br J Psychiatry*. 1993;162:272–273.
56. Clarke M, Moran P, Keogh F, et al. Seasonal influences on admissions in schizophrenia and affective disorder in Ireland. *Schizophr Res*. 1998;34(3):143–149.
57. 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. *Eur Psychiatry*. 1999;14(5):251–255.
58. Shiloh R, Shapira A, Potchter O, et al. Effects of climate on admission rates of schizophrenia patients to psychiatric hospitals. *Eur Psychiatry*. 2005;20(1):61–64.
59. Tian WH, Lee HC, Liu TC, et al. Seasonal variation in schizophrenia admissions in a Chinese population. *Schizophr Res.* 2006;86(1–3):333–334.
60. Aviv A, Bromberg G, Baruch Y, et al. The role of environmental influences on schizophrenia admissions in Israel. *Int J Soc Psychiatry.* 2011;57(1):57–68.
61. Amr M, Volpe FM. Seasonal influences on admissions for mood disorders and schizophrenia in a teaching psychiatric hospital in Egypt. *J Affect Disord*. 2012;137(1–3):56–60.
62. Davies G, Ahmad F, Chant D, et al. Seasonality of first admissions for schizophrenia in the Southern Hemisphere. *Schizophr Res*. 2000;41(3):457–462.
63. Owens N, McGorry PD. Seasonality of symptom onset in first-episode schizophrenia. *Psychol Med*. 2003;33(1):163–167.
64. Daniels BA, Kirkby KC, Mitchell P, et al. Seasonal variation in hospital admission for bipolar disorder, depression and schizophrenia in Tasmania. *Acta Psychiatr Scand*. 2000;102(1):38–43.
65. Saha S, Chant DC, Welham JL, et al. The incidence and prevalence of schizophrenia varies with latitude. *Acta Psychiatr Scand*. 2006;114(1):36–39.
66. Torrey EF, Miller J, Rawlings R, et al. Seasonality of births in schizophrenia and bipolar disorder: a review of the literature. *Schizophr Res*. 1997;28(1):1–38.
67. Pjrek E, Winkler D, Heiden A, et al. Seasonality of birth in seasonal affective disorder. *J Clin Psychiatry*. 2004;65(10):1389–1393.
68. McGrath J. Hypothesis: is low prenatal vitamin D a risk-modifying factor for schizophrenia? *Schizophr Res*. 1999;40(3):173–177.
69. Wortsman J, Matsuoka LY, Chen TC, et al. Decreased bioavailability of vitamin D in obesity. *Am J Clin Nutr*. 2000;72(3):690–693.
70. Vimaleswaran KS, Berry DJ, Lu C, et al; Genetic Investigation of Anthropometric Traits-GIANT Consortium. Causal relationship between obesity and vitamin D status: bi-directional Mendelian randomization analysis of multiple cohorts. *PLoS Med*. 2013;10(2):e1001383.

See supplementary material for this article at PSYCHIATRIST.COM.

THE JOURNAL OF
CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: Seasonality Shows Evidence for Polygenic Architecture and Genetic Correlation With Schizophrenia and Bipolar Disorder

Author(s): Enda M. Byrne, PhD; Uttam K. Raheja, MD; Sarah H. Stephens, PhD; Andrew C. Heath, DPhil; Pamela A. F. Madden, PhD; for the Psychiatric Genetics Consortium Major Depressive Disorder Working Group; Dipika Vaswani, MD; Gagan V. Nijjar, MD; Kathleen A. Ryan, MS; Hassaan Youssufi, BSc; Philip R. Gehrman, PhD; Alan R. Shuldiner, MD; Nicholas G. Martin, PhD; Grant W. Montgomery, PhD; Naomi R. Wray, PhD; Elliot C. Nelson, MD; Braxton D. Mitchell, PhD; and Teodor T. Postolache, MD

DOI Number: 10.4088/JCP.14m08981

List of Supplementary Material for the article

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Material

Supplementary eTable 4. List of contributors to PGC-MDD GWAS study

Study	***Title***	***First name***	***Last name***	***Affiliation***	
mpip, mdd2000, statistical genetics	Dr	Stephan	Ripke	Harvard University/Broad Institute	USA
QIMR, mdd2000, statistical genetics	Dr	Naomi R	Wray	Queensland Institute of Medical Research/University of Queensland	Australia
radiant, statistical genetics	Prof	Cathryn M	Lewis	Institute of Psychiatry, King's College London	UK
stard	Assoc Prof	Steven P	Hamilton	University of California, San Francisco	USA
genred, GenRED2, DepGenesNetworks	Prof	Myrna M	Weissman	Columbia University	USA
radiant	Dr	Gerome	Breen	Institute of Psychiatry, King's College London	UK
statistical genetics	Dr	Enda M	Byrne	Queensland Institute of Medical Research	Australia
mdd2000	Prof	Douglas HR	Blackwood	University of Edinburgh	UK
gain, mdd2000	Prof	Dorret I	Boomsma	VU University, Amsterdam	The Netherlands
boma	Prof	Sven	Cichon	University of Bonn	Germany
QIMR, mdd2000	Prof	Andrew C	Heath	Washington University, St Louis	USA
mpip, gsk	Prof	Florian	Holsboer	Max Planck Institute of Psychiatry	Germany
mpip	Dr	Susanne	Lucae	Max Planck Institute of Psychiatry	Germany
QIMR, mdd2000	Prof	Pamela AF	Madden	Washington University, St Louis	USA
QIMR, mdd2000	Prof	Nicholas G	Martin	Queensland Institute of Medical Research	Australia
radiant	Prof	Peter	McGuffin	Institute of Psychiatry, King's College London	UK
gsk, radiant	Dr	Pierandrea	Muglia	GlaxoSmithKline	Italy
boma	Prof	Markus M	Noethen	University of Bonn	Germany
gain, mdd2000	Prof	Brenda P	Penninx	VU University Medical Center, Amsterdam	The Netherlands
QIMR, mdd2000	Dr	Michele L	Pergadia	Washington University, St Louis	USA
genred, GenRED2,	Prof	James B	Potash	University of Iowa	USA

DepGenesNetworks					
boma	Prof	Marcella	Rietschel	Central Inst Mental Health, University of Heidelberg	Germany
gain, statistical genetics	Prof	Danyu	Lin	University of North Carolina	USA
mpip	Prof	Bertram	Müller-Myhsok	Max Planck Institute of Psychiatry	Germany
genred, GenRED2, DepGenesNetworks	Dr	Jianxin	Shi	National Cancer Institute	USA
deCODE	Dr	Stacy	Steinberg	deCODE Genetics	Iceland
SHIP-LEGEND	Prof	Hans J	Grabe	University of Greifswald	Germany
TwinGene	Prof	Paul	Lichtenstein	Karolinska Institutet	Sweden
TwinGene	Dr	Patrik	Magnusson	Karolinska Institutet	Sweden
Harvard i2b2	Assoc Prof	Roy H	Perlis	Massachusetts General Hospital	USA
PsyCoLaus	Prof	Martin	Preisig	University of Lausanne	Switzerland
Harvard i2b2	Assoc Prof	Jordan W	Smoller	Massachusetts General Hospital	USA
deCODE	Dr	Kari	Stefansson	deCODE Genetics	Iceland
genpod	Dr	Rudolf	Uher	Institute of Psychiatry, King's College London	UK
PsyCoLaus	Dr	Zoltan	Kutalik	University of Lausanne	Switzerland
genpod	Dr	Katherine E	Tansey	Institute of Psychiatry, King's College London	UK
SHIP-LEGEND	Dr	Alexander	Teumer	University of Greifswald	Germany
TwinGene		Alexander	Viktorin	Karolinska Institutet	Sweden
radiant	Dr	Michael R	Barnes	GlaxoSmithKline	UK
mpip	Dr	Thomas	Bettecken	Max Planck Institute of Psychiatry	Germany
mpip	Dr	Elisabeth B	Binder	Max Planck Institute of Psychiatry	Germany
boma		René	Breuer	Central Inst Mental Health, University of Heidelberg	Germany
Harvard i2b2		Victor M	Castro	Partners HealthCare System	USA
Harvard i2b2	Dr	Susanne E	Churchill	Partners HealthCare System	USA
genred, GenRED2	Prof	William H	Coryell	University of Iowa	USA
radiant	Prof	Nick	Craddock	Cardiff University	UK

radiant	Prof	Ian W	Craig	Institute of Psychiatry, King's College London	UK
mpip	Dr	Darina	Czamara	Max Planck Institute of Psychiatry	Germany
gain, mdd2000	Prof	Eco J	De Geus	VU University, Amsterdam	The Netherlands
boma		Franziska	Degenhardt	University of Bonn	Germany
radiant	Prof	Anne E	Farmer	Institute of Psychiatry, King's College London	UK
Harvard i2b2	Prof	Maurizio	Fava	Massachusetts General Hospital	USA
boma		Josef	Frank	Central Inst Mental Health, University of Heidelberg	Germany
Harvard i2b2		Vivian S	Gainer	Partners HealthCare System	USA
Harvard i2b2		Patience J	Gallagher	Massachusetts General Hospital	USA
QIMR, mdd2000	Dr	Scott D	Gordon	Queensland Institute of Medical Research	Australia
Harvard i2b2		Sergey	Goryachev	Partners HealthCare System	USA
boma		Magdalena	Gross	University of Bonn	Germany
genpod	Dr	Michel	Guipponi	University of Geneva	Switzerland
QIMR, mdd2000		Anjali K	Henders	Queensland Institute of Medical Research	Australia
boma		Stefan	Herms	University of Bonn	Germany
QIMR, mdd2000	Prof	Ian B	Hickie	University of Sydney, Sydney	Australia
boma		Susanne	Hoefels	University of Bonn	Germany
gain	Prof	Witte	Hoogendijk	Erasmus Medical Center	The Netherlands
gain, mdd2000	Dr	Jouke Jan	Hottenga	VU University, Amsterdam	The Netherlands
Harvard i2b2	Assoc Prof	Dan V	Iosifescu	Massachusetts General Hospital	USA
mpip	Dr	Marcus	Ising	Max Planck Institute of Psychiatry	Germany
radiant	Dr	Ian	Jones	Cardiff University	UK
radiant	Dr	Lisa	Jones	University of Birmingham	UK
gain	Assoc Prof	Tzeng	Jung-Ying	North Carolina State University	USA
genred, GenRED2	Prof	James A	Knowles	University of Southern California	USA

Harvard i2b2	Prof	Isaac S	Kohane	Brigham and Women's Hospital	USA
mpip	Dr	Martin A	Kohli	Max Planck Institute of Psychiatry	Germany
radiant	Dr	Ania	Korszun	Queen Mary University of London	UK
TwinGene	Dr	Mikael	Landen	Karolinska Institutet	Sweden
genred, GenRED2	Prof	William B	Lawson	Howard University	USA
genpod	Prof	Glyn	Lewis	University of Bristol	UK
mdd2000	Dr	Donald	MacIntyre	University of Edinburgh	UK
boma	Prof	Wolfgang	Maier	University of Bonn	Germany
boma	Dr	Manuel	Mattheisen	University of Bonn	Germany
stard	Prof	Patrick J	McGrath	Columbia University	USA
mdd2000	Dr	Andrew	McIntosh	University of Edinburgh	UK
mdd2000	Dr	Alan	McLean	University of Edinburgh	UK
gain, mdd2000	Dr	Christel M	Middeldorp	VU University, Amsterdam	The Netherlands
radiant	Dr	Lefkos	Middleton	Imperial College	UK
QIMR, mdd2000	Prof	Grant M	Montgomery	Queensland Institute of Medical Research	Australia
Harvard i2b2	Asst Prof	Shawn N	Murphy	Massachusetts General Hospital	USA
SHIP-LEGEND	Prof	Matthias	Nauck	University of Greifswald	Germany
gain, mdd2000	Prof	Willem A	Nolen	Groningen University Medical Center	The Netherlands
QIMR, mdd2000	Dr	Dale R	Nyholt	Queensland Institute of Medical Research	Australia
genpod	Prof	Michael	O'Donovan	Cardiff University	UK
deCODE	Dr	Högni	Oskarsson	Therapeia, University Hospital	Iceland
TwinGene	Dr	Nancy	Pedersen	Karolinska Institutet	Sweden
genred, GenRED2	Prof	William A	Scheftner	Rush University Medical Center	USA
SHIP-LEGEND		Andrea	Schulz	University of Greifswald	Germany
boma	Prof	Thomas G	Schulze	University of Goettingen	USA

stard	Asst Prof	Stanley I	Shyn	University of Washington	USA
deCODE	Dr	Engilbert	Sigurdsson	Landspitali University Hospital	Iceland
stard	Assoc Prof	Susan L	Slager	Mayo Clinic	USA
gain, mdd2000	Prof	Johannes H	Smit	VU University Medical Center, Amsterdam	The Netherlands
deCODE	Dr	Hreinn	Stefansson	deCODE Genetics	Iceland
boma	Dr	Michael	Steffens	University of Bonn	Germany
deCODE	Dr	Thorgeir	Thorgeirsson	deCODE Genetics	Iceland
gsk	Dr	Federica	Tozzi	GlaxoSmithKline	Italy
boma	Dr	Jens	Treutlein	Central Inst Mental Health, University of Heidelberg	Germany
mpip	Dr	Manfred	Uhr	Max Planck Institute of Psychiatry	Germany
mdd2000	Prof	Edwin JCG	van den Oord	Virginia Commonwealth University	USA
gain, mdd2000		Gerard	Van Grootheest	VU University Medical Center, Amsterdam	The Netherlands
SHIP-LEGEND	Prof	Henry	Völzke	University of Greifswald	Germany
Harvard i2b2	Dr	Jeffrey B	Weilburg	Massachusetts General Hospital	USA
gain, mdd2000	Dr	Gonneke	Willemsen	VU University, Amsterdam	The Netherlands
gain, mdd2000	Prof	Frans G	Zitman	Leiden University Medical Center, Leiden	The Netherlands
statistical genetics	Dr	Benjamin	Neale	Harvard University/Broad Institute	USA
statistical genetics	Assoc Prof	Mark	Daly	Harvard University/Broad Institute	USA
genred, GenRED2, DepGenesNetworks	Prof	Douglas F	Levinson	Stanford University	USA
gain, mdd2000	Prof	Patrick F	Sullivan	University of North Carolina	USA

Supplementary Methods

QIMR Genotyping and Imputation

Genotype information was collected as part of a number of genotyping projects undertaken at QIMR. DNA samples were collected in accordance with standard protocols and submitted to different genotype centres using different SNP platforms (Illumina 317K, IlluminaHumanCNV370- Quadv3, and Illumina Human 610-Quad). SNPs were called using the Illumina BeadStudio software. A standard quality control (QC) procedure was applied to each project individually, prior to imputation. A detailed description of the QC steps and procedure for detection of ancestry outliers is given elsewhere (Medland et al., 2009).

A set of 274,604 SNPs that were common to all of the genotyping chips was used for imputation, which was performed using the program MACH.(Li et al., 2009) The imputed SNPs were screened further for Mendelian errors, minor allele frequency and missingness. Only SNPs with an imputation quality score (R2) greater than 0.3 were retained,

Results of GWAS meta-analysis

There was little evidence of population stratification in any of the analyses. The lambda inflation factor for the GWAS in the Australian population was 1.00, and the same value was found for the meta-analysis of the Australian and Amish results. Lambda was equal to 1.03 in the Amish analysis (Supplementary Figure 1-3).

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. This region has not been implicated in mood disorders previously. Other SNPs that show the greatest evidence of

association with the GSS include rs13257657, a SNP found in a region encoding a microRNA (mir-1204). The microRNA.org software predicts that mir-1204 may potentially target a wide range of genes, (Betel et al., 2008), with the strongest evidence for the *MYLK* gene as a target.

Another SNP - rs1808478 – also shows evidence of association ($p = 4.7 \times 10^{-4}$, $\beta = -0.59$, S.E. = 0.13. This SNP is found in the *POLR2M* gene, which encodes a subunit of the RNA polymerase II complex. This gene is also a homolog of the ionotropic glutamate receptor N-methyl D-aspartate, indicating that it may play a role in signalling the brain.

Estimating Phenotypic Variance Explained by all SNPs

A whole-genome method that estimates the genetic variance explained by all SNPs on the chips (Yang et al.), implemented in the freely available GCTA software (Yang et al., 2011) was utilised. The Amish sample was not included in this analysis. Initially, one individual per family was selected at random from the Australian sample (n = 1,999) individuals. Only genotyped SNPs were utilised. A set of quality control steps were implemented to remove SNPs with high rates of missingness or Hardy-Weinberg Equilibrium p-value < 0.001. After quality control, a total of 217,053 SNPs remained. Individuals with more than 1% missing SNPs (n = 44) were removed. To ensure that there was no cryptic relatedness in the sample that could bias the results, individuals with a pairwise genetic relatedness coefficient as estimated from the SNPs of more than 0.025 were removed. After QC steps, a total of 1,864 individuals remained. The estimated proportion of the variance explained was 8.6% with a standard error of 20.0%. Including the genetic component estimated from the SNPs did not significantly improve the fit of the model, when compared to including only environmental effects (p = 0.30). The large

standard error of the estimate indicates that larger sample sizes are needed in order to have adequate power to reject the null hypothesis that common variants on the SNP chips explain a proportion of the heritability of seasonality.

BETEL, D., WILSON, M., GABOW, A., MARKS, D. S. & SANDER, C. (2008). The microRNA.org resource: targets and expression. *Nucleic Acids Res,* 36**,** D149-153.

LI, Y., WILLER, C., SANNA, S. & ABECASIS, G. (2009). Genotype imputation. *Annu Rev Genomics Hum Genet,* 10**,** 387-406.

MEDLAND, S. E., NYHOLT, D. R., PAINTER, J. N., MCEVOY, B. P., MCRAE, A. F., ZHU, G., GORDON, S. D., FERREIRA, M. A., WRIGHT, M. J., HENDERS, A. K., CAMPBELL, M. J., DUFFY, D. L., HANSELL, N. K., MACGREGOR, S., SLUTSKE, W. S., HEATH, A. C., MONTGOMERY, G. W. & MARTIN, N. G. (2009). Common variants in the trichohyalin gene are associated with straight hair in Europeans. *Am J Hum Genet,* 85**,** 750-755.

YANG, J., BENYAMIN, B., MCEVOY, B. P., GORDON, S., HENDERS, A. K., NYHOLT, D. R., MADDEN, P. A., HEATH, A. C., MARTIN, N. G., MONTGOMERY, G. W., GODDARD, M. E. & VISSCHER, P. M. Common SNPs explain a large proportion of the heritability for human height. *Nat Genet,* 42**,** 565-569.

YANG, J., LEE, S. H., GODDARD, M. E. & VISSCHER, P. M. (2011). GCTA: a tool for genome-wide complex trait analysis. *Am J Hum Genet,* 88**,** 76-82.

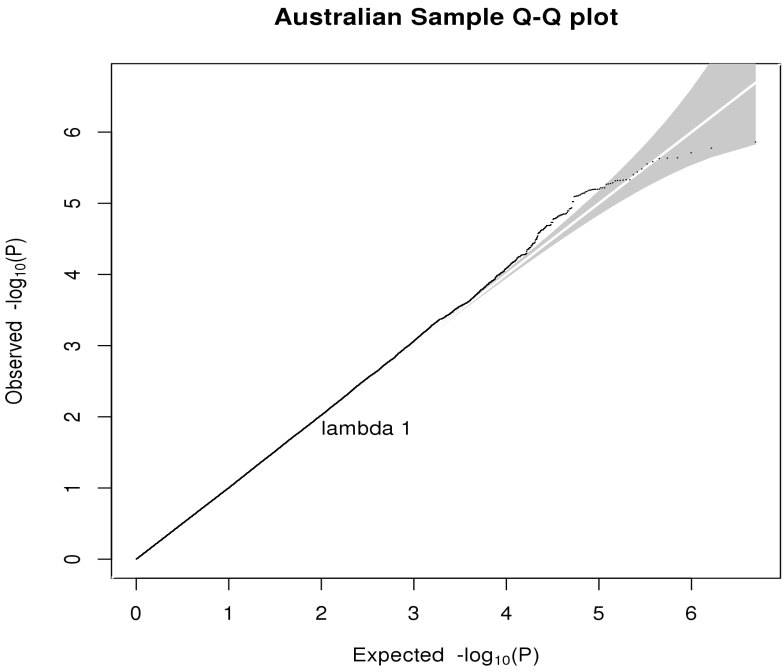
Supplementary eTable 1. The most significant SNPs in the Australian sample and their corresponding results in the Amish sample.

SNP	P	CHR	coordinate	Tested Allele	Freq	Beta	S.E.	closest gene	distance to gene	MAF in Amish	Beta Amish	S.E. Amish	P Amish
rs12411769	1.38E-06	10	124969001	C	0.04	1.87	0.39	LOC100131719	-18669	0.02	0.17	1.65	0.91
rs9555488	1.67E-06	13	109254277	T	0.29	-0.54	0.11	MYO16	0	0.13	-0.03	0.29	0.91
rs1813849	1.95E-06	2	200142847	T	0.12	0.81	0.17	SATB2	0	0.07	-0.69	0.43	0.11
rs13257657	4.72E-06	8	128986335	C	0.13	0.84	0.18	MIR1204;PVT1	0	0.04	-0.79	0.57	0.16
rs31019	5.14E-06	5	96422368	T	0.45	0.50	0.11	LIX1	-2411	0.46	-0.09	0.20	0.66
rs7870657	5.37E-06	9	71724126	G	0.38	0.49	0.11	FXN	9032	0.49	-0.19	0.19	0.31
rs2498436	6.50E-06	9	71790905	G	0.29	0.52	0.12	TJP2	0	0.32	0.03	0.20	0.89
rs1808478	7.18E-06	15	58009759	T	0.18	-0.60	0.13	GCOM2	0	0.10	-0.48	0.58	0.41
rs3936510	7.22E-06	5	55860866	T	0.19	0.59	0.13	OTTHUMG00000059482	0	0.16	-0.02	0.27	0.93
rs379533	7.83E-06	1	30483596	T	0.46	-0.47	0.11	OTTHUMG00000003683	3203	0.35	0.34	0.20	0.08

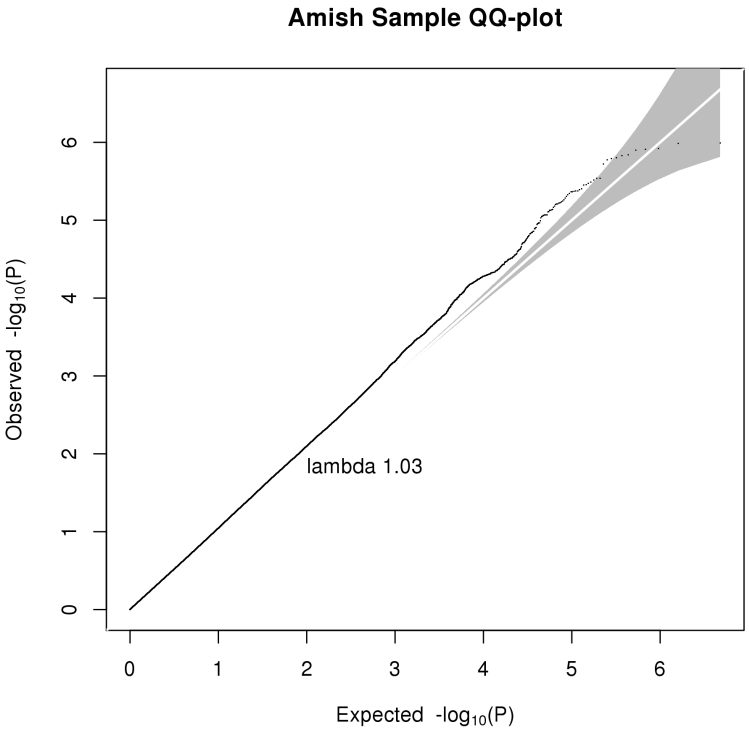
Supplementary eTable 2. Independent SNPs with $p < 10^{-5}$ from meta-analysis of cohorts

SNP	CHR	coordinate	Meta_Pval	Meta_Beta	META_SE	closest gene	distance to gene	Tested Allele	Non-tested Allele	Direction	Freq_Amish	Freq_QIMR	Pval_Amish	Pval_QIMR
rs11825064	11	134477854	1.70E-06	0.64	0.13	OTTHUMG00000165125	34904	c	g	++	0.19	0.15	2.30E-04	9.28E-04
rs13257657	8	128986335	1.73E-06	-0.83	0.17	MIR1204;PVT1	0	t	c	--	0.04	0.13	1.61E-01	4.72E-06
rs12411769	10	124969001	2.30E-06	-1.78	0.38	OTTHUMG00000019196	-37606	a	c	--	0.98	0.96	9.18E-01	1.38E-06
rs1808478	15	58009759	4.68E-06	-0.59	0.13	GCOM2;POLR2M	0	t	c	--	0.90	0.82	4.09E-01	7.18E-06
rs9559377	13	109264870	5.01E-06	0.49	0.11	MYO16	0	a	t	++	0.86	0.73	6.88E-01	2.80E-06
rs196889	8	24734677	6.40E-06	0.68	0.15	OTTHUMG00000163790	0	t	c	++	0.87	0.91	1.68E-03	9.44E-04
rs1131351	2	204023800	7.51E-06	0.51	0.11	SDC1	0	c	g	++	0.66	0.59	1.31E-02	1.54E-04
rs7870657	9	71724126	8.56E-06	-0.41	0.09	FXN	9032	a	g	--	0.49	0.62	3.09E-01	5.37E-06

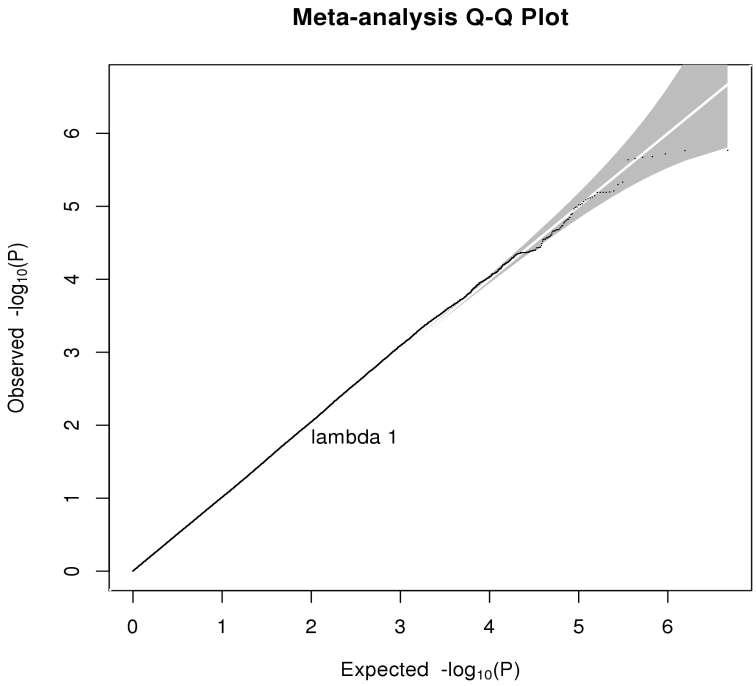
Supplementary eFigure 1. Q-Q plot from Australian GWAS analysis



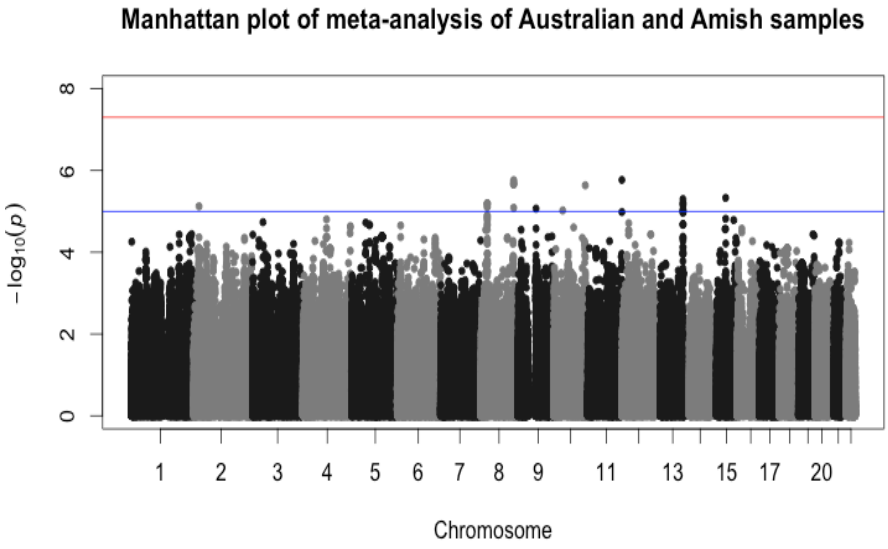
Supplementary eFigure 2. Q-Q plot from GWAS analysis in Amish sample



Supplementary eFigure 3. Q-Q plot for meta-analysis



Supplementary eFigure 4. Manhattan Plot for meta-analysis



Supplementary eTable 3. Results of profile scoring analyses using results from Psychiatric Genetics Consortium GWAS of schizophrenia, bipolar disorder and Major Depressive Disorder

BIP SNP significance cutoff	No. of Alleles	Adjusted R2	p-value for model
p < 0.001	737	0.002	2.95E-02
p < 0.01	4060	0.002	1.66E-02
p < 0.1	24096	0.004	4.40E-03
p < 0.5	77395	0.004	3.38E-03
All SNPs	108832	0.003	5.85E-03
MDD SNP significance cutoff	**No. of Alleles**	**Adjusted R2**	**p-value for model**
0.001	310	0	0.52
0.01	2743	0	0.25
0.1	20586	0	0.10
0.5	83047	0	0.32
All SNPs	154538	0	0.29
SCZ SNP significance cutoff	**No. of Alleles**	**Adjusted R2**	**p-value for model**
0.001	427	0.004352352	1.83E-03
0.01	3348	0.016183205	6.86E-09
0.1	23610	0.025636295	3.60E-13
0.5	83903	0.0308183	1.61E-15
All SNPs	123040	0.030867498	1.53E-15