Aus dem Institut für Psychiatrische Phänomik und Genomik Klinikum, LMU Klinikum und der Klinik für Psychiatrie und Psychotherapie der Ludwig-Maximilians-Universität München

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Genetic characterization of Age and Polarity at Onset in Bipolar Disorder

vorgelegt von:

dr. med. Janos Kalman

aus:

Szeged, Ungarn

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First evaluator (1. TAC member): Prof. Dr. Thomas G. Schulze
Second evaluator (2. TAC member): Prof. Dr. Peter Falkai
Third evaluator: Prof. Dr. Maria Colomé-Tatché
Fourth evaluator: Prof. Dr. Peter Brieger

Dean: **Prof. Dr. med. Thomas Gudermann**

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List of abbreviations

BD Bipolar Disorder

DSM Diagnostic and Statistical Manual of Mental Disorders

GWAS Genome-wide Association Study

h^2_{SNV} SNV-based heritability

ICD International Classification of Diseases

MD Major Depression

PGC Psychiatric Genomics Consortium

PGS Polygenic score

PRS Polygenic risk score

SNV Single Nucleotide Variant

SZ Schizophrenia

1. Introductory summary

1.1. Bipolar Disorder

Bipolar Disorder (BD) is a chronic mental health disorder, affecting 2-3% of the population (Merikangas et al., 2011). Its symptoms include recurrent episodes of elated or irritated mood, overconfidence, grandiosity, talkativeness, (extreme) disinhibition, decreased need for sleep, and increased energy and activity (hypomania or mania), and depressed mood and reduced energy and activity (depression) (Carvalho et al., 2020). BD has two major subtypes, bipolar disorder type 1 which is characterized by alternating episodes of mania and depression, and bipolar disorder type 2, characterized by the occurrence of at least one hypomanic and one depressive episode. The disease course of BD is heterogeneous, and most patients show substantial illness-related disability, (co-)morbidity, and mortality, resulting in increased health care utilization and reduced psychosocial functioning (Bauer et al., 2018). This highlights the necessity of early diagnosis and intervention, for which a better understanding of the factors influencing the development and clinical course of BD is a prerequisite.

The development and clinical course of BD are influenced by an interplay of genetic and environmental risk factors (Carvalho et al., 2020; Vieta et al., 2018). The estimated 60-80% heritability of BD suggests that genetics play a prominent role in shaping the individual vulnerability of BD (Mullins et al., 2021). Genome-wide association studies (GWAS) have, so far, identified 64 risk variants for BD, which were enriched in genes in synaptic and calcium signaling pathways and brain-expressed genes (Mullins et al., 2021). Genetic analyses also provide evidence that the century-old clinical observations of a symptomatic overlap across the affective and psychosis spectrum are partly due to molecular factors transdiagnostically influencing psychiatric disorders, e.g., via shared risk variants with pleiotropic effects (Lee et al., 2019; Ruderfer et al., 2018). Several of the BD-associated GWAS signals have previously been implicated in schizophrenia (SZ)

or major depression (MD), and there is a significant genetic correlation between these conditions (r_g=0.68 and r_g=0.44, respectively) (Mullins et al., 2021; Ruderfer et al., 2018). In total, the phenotypic variance explained by common genetic variants (SNV-based heritability, h^2_{SNV}) is 18% (Mullins et al., 2021). However, although GWAS increased our understanding of the genetic etiology of BD, the majority of the BD-associated risk variants are yet to be identified (Mullins et al., 2021). Interestingly, despite the comparable GWAS sample size, prevalence, and heritability estimates, currently fewer genome-wide significant loci have been identified for BD than for SZ, most probably due to the extensive clinical heterogeneity of BD (Mullins et al., 2021; Ripke et al., 2014). Therefore, reducing the phenotypic heterogeneity by stricter phenotype definitions and focusing on clinically relevant subphenotypes, e.g., the presence of psychotic symptoms, suicidality, cognitive symptoms, and the age and polarity at onset has become one of the major goals of the field.

1.2. The clinical relevance of the disease onset phenotypes

Individuals usually experience their first (hypo)manic or depressive illness episode in adolescence or early adulthood, a period that is essential for their psychosocial development. The on average, 5-10 years delay between the first symptom presentation and the correct diagnosis compounds the problem (Dagani et al., 2017).

Diagnostic and treatment delay can be especially long for patients with a depressive index (i.e., first) episode (Smith et al., 2011). Current diagnostic criteria cannot differentiate between the symptoms of unipolar depression and bipolar depressive episodes, thus BD patients with a depressive index episode are often misdiagnosed and treated for MD until they experience their first (hypo)manic episode (Leonpacher et al., 2015; Young and Macpherson, 2011). Since depression is the most prevalent presenting polarity in BD, the misdiagnosis can impact as much as 40% of the patients diagnosed with BD (Baldessarini et al., 2020). The interval between the onset of symptoms and the initiation of adequate treatment is important because treatment

delays are associated with a more disadvantageous disease course including chronic, recurrent mood episodes, increased rates of subsyndromal symptoms, greater psychosocial impairment, and higher healthcare cost (Dagani et al., 2017; Young and Macpherson, 2011).

Patients with an early-onset BD have a more severe disease course: they experience psychotic symptoms and illness episodes more frequently, show a higher suicide rate, lower functioning, and more comorbid conditions (Perlis et al., 2004; Van Bergen et al., 2019). Based on these observations, it has been widely hypothesized that early disease onset is an expression of a more severe disease risk and stratifying patients by age at onset would help in narrowing down the molecular heterogeneity of BD and of other disorders (Hagenaars et al., 2020; Kalman et al., 2019; Power et al., 2017). Therefore, the age at illness onset has been considered a suitable phenotype for genetic studies. Genetic risk loci associated with the age at onset have already been identified for multiple sclerosis, Alzheimer's disease, and MD (Andlauer et al., 2016; Naj et al., 2014; Power et al., 2017).

It has also been suggested that the genetics of early disease onset BD may be quantitatively and qualitatively different from late-onset BD (Kennedy et al., 2015). However, evidence for a distinctive genetic profile of early- vs. late-onset BD is inconclusive. Family studies have shown an accumulation of early-onset cases in BD multiplex families, suggesting that shared genetic and/or environmental factors influence the age at disease onset (Kennedy et al., 2015). Thus far, GWAS studies for age at BD onset have been underpowered and yielded no significant findings (Belmonte Mahon et al., 2011; Jamain et al., 2014).

The coordinated efforts of international consortia like the International Consortium on Lithium Genetics (ConLiGen) and the Psychiatric Genomics Consortium (PGC) have significantly increased the amount of available data and created a unique opportunity to investigate the genetics of illness onset in BD at an unprecedented scale (Schulze et al., 2010; Sullivan et al., 2018). Therefore, the phenotypic and genetic dissection of the disease onset phenotypes (age and polarity at onset) in BD has been the major focus of my Ph.D. work.

1.3. Investigating the association between bipolar and schizophrenia polygenic risk and age at disease onset in bipolar disorder

Kalman, J.L. [*]***,*** *Papiol, S.* [*]*, Forstner, A.J.* [*]*, [...], Nöthen, M., Rietschel, M., Schulze, T.G. (2018). Investigating polygenic burden in age at disease onset in bipolar disorder: Findings from an international multicentric study. Bipolar Disord, 21(1), 68-75. doi:10.1111/bdi.12659*

According to the results of large genomic studies, the genetic architecture of complex psychiatric (and non-psychiatric) disorder-related phenotypes, including the age at onset, is very likely to be polygenic and influenced by several thousands of genetic variants (Anttila et al., 2018; Mullins et al., 2021; Sullivan et al., 2018). Although the contribution of each variant is minuscule (most common genetic variants associated with common psychiatric disorders have odds ratios (OR) below 1.05), these variants can cumulatively explain a significant proportion of the phenotypic variance. The cumulative polygenic load of an individual can be expressed as a polygenic score (PGS), also known as polygenic risk score (PRS). PGS are calculated using the summary statistics of GWAS of independent training samples as weights and can be used to quantify the cumulative genetic risk an individual carries. Thus, they may have potential clinical utility for patient stratification and risk prediction in the future.

Accumulating evidence demonstrates that genetic variants associated with the risk of mental health disorders also influence the clinical manifestation of the disease (Allardyce et al., 2018; Guzman-Parra et al., 2021; Meier et al., 2016; Ruderfer et al., 2018; Wray et al., 2018), for example, the number of episodes/hospitalizations in SZ and MD, the age at onset of MD, and the presence of psychotic symptoms in BD (Allardyce et al., 2018; Meier et al., 2016; Ruderfer et al., 2018; Wray et al., 2018). However, the association between BD- and SZ-PGS and the age at BD onset has previously only been investigated in a very small (N=285) sample (Aminoff et al., 2015).

Therefore, in our first study, we examined the association between SZ- and BD-PGS and the age at onset using the latest GWAS summary statistics datasets available at the time of the study

(PGC-SZ2 and PGC-BD) (Ripke et al., 2014; Sklar et al., 2011). The study was conducted on n=1995 patients with a lifetime DSM-III and DSM-IV diagnosis of BD type 1. Patients were recruited at 21 study sites across Europe (Austria, Czech Republic, Italy, France, Germany, Poland, Romania, Spain, and Sweden), North America (Canada and USA), and Australia (Budde et al., 2019; Schulze et al., 2010).

In line with the liability-threshold model of polygenic traits, which suggests that individuals with more disease-associated genetic variants can be expected to cross the liability threshold earlier and thus have earlier disease onset, we hypothesized that increased BD- and SZ-PGS will be associated with an earlier disease onset in BD (Gottesman and Shields, 1967). However, the investigated PGS were not significantly associated with the age at onset, regardless of using a continuous or categorical (childhood (≤12 years), adolescence (13- 18 years), or adulthood (>18 years)) age at onset definition. This finding suggested that, despite the almost tenfold increase in sample size compared to the previous study, we either still lacked sufficient statistical power for detecting any underlying genetic association or the age at onset in BD is not shaped by common variants associated with risk of psychiatric disorders (Aminoff et al., 2015). However, the latter assumption is improbable given the findings for other disorders (Naj et al., 2014; Power et al., 2017; Wray et al., 2018).

Interestingly, and in line with previous observations, we observed a significantly lower age at onset in patients recruited in the USA in comparison to those from Europe, Australia, and Canada (mean ± SD: 19.25 ± 9.55 and 25.92 ± 10.33 years, respectively, $P < 2.25 \times 10^{-26}$) (Post et al., 2008). This result suggests that variation due to cultural and/or organizational differences between the individual sites and continents might influence the age at onset and/or phenotype definitions and thus potentially reduce statistical power for genetic analyses. We attempted to control for this issue by using site, genotyping chip, and ancestry principal components as covariates. Furthermore, as a secondary sensitivity analysis, we also conducted separate regression analyses for the USA and the rest of the world. These analyses provided similar results.

1.4. Characterization of Age and Polarity at Onset in Bipolar Disorder

***Kalman, J.L.**[*]*, *Olde Loohuis L.[*], Vreeker A.[*], [...], Andlauer T.F.M.[+], Schulze T.G.[+], Ophoff R.[+], (2021). Characterization of Age and Polarity at Onset in Bipolar Disorder. The British Journal of Psychiatry, in press*

The power to detect risk variants increases with sample size. For example, the number of BD-associated risk variants increased from 4 to 30 and 64 as the sample size (cases and controls) increased from 16,731 to 51,710 and to 413,466 subjects (Mullins et al., 2021; Sklar et al., 2011; Stahl et al., 2019). A comparable increase has been observed for SZ and MD (Ripke et al., 2020; Wray et al., 2018). Interestingly, the cross-disorder group of the PGC described a nominally significant association between SZ-PGS and the age at onset in BD in a sample of 8610 BD patients (OR=-3.36, $p = 7.9\times10^{-4}$; significance threshold corrected for multiple testing by Bonferroni's method, $\alpha = 4.47\times10^{-4}$) (Ruderfer et al., 2018).

Therefore, for our next study we collected phenotypic and genetic data from almost 15,000 BD patients and thus increased our sample size significantly compared to the first study described above. Furthermore, as an attempt to control for potential bias introduced by sample and phenotype heterogeneity, we collected detailed information on the disease onset phenotypes, including the polarity at onset and the method used to assess the age at onset. Moreover, we combined the analyses of the individual cohorts using inverse variance-weighted meta-analysis. By analyzing the genetics of polarity at onset for the first time, we hoped to gain important insights into the pathophysiology of disease development and potentially identify genetic markers which differentiate between patients with a depressive and (hypo)manic polarity at onset (i.e., having either mania or depression upon illness presentation).

Our study constitutes the largest study conducted so far to systematically characterize age (N=12977) and polarity (N=6773) at onset in BD. We highlighted the clinical relevance of age and polarity at onset and replicated findings of previous studies. Importantly, we demonstrated that

of lifetime delusions, hallucinations, suicide attempts, suicidal ideation, lower educational attainment, and not living together were associated with age at onset, whereas higher probability of suicidal ideation and lifetime suicide attempts (with depressive illness onset) and delusions and number of manic episodes with a (hypo)manic onset.

We found significant heterogeneity of the age at onset (and, partly, the polarity at onset) phenotype across cohorts, continents, and age-at-onset definitions. Thus, our results underscore the challenges for genetic analyses in the presence of substantial phenotypic heterogeneity. First, heritability estimates varied for different criteria used to define the age at onset and decreased when combining multiple cohorts. Second, a single genome-wide significant variant, identified in the age-at-onset discovery GWAS, did not replicate in an independent (N=2,237) dataset. Still, analyses of PGS showed that increased PGS for autism spectrum disorder (β=-0.34 years per unit increase in PGS, SE=0.08, $P=9.85\times10^{-6}$, significance threshold corrected for multiple testing by Bonferroni's method, $\alpha = 5.2\times10^{-4}$), MD (β=-0.34, SE=0.08, $P=1.40\times10^{-6}$), SZ (β=-0.39, SE=0.08, $P=2.91\times10^{-6}$), and educational attainment (β=-0.31, SE=0.08, $P=5.58\times10^{-5}$) are associated with an early age at BD onset, providing evidence that the age at onset is influenced by a broad liability to mental health disorders. Interestingly, although we observed significant h^2_{SNV} for the polarity at onset, we were not able to identify significant associations with the PAO in neither GWAS nor PGS analyses.

1.5. Summary and outlook

In summary, our results extend our knowledge on the genetic architecture of BD onset. They provide evidence that BD patients with an earlier age at onset have a distinctive phenotypic and genetic profile and that an early disease onset can indeed be viewed as a more severe expression of disease risk. However, the low estimated heritability, the lack of replication of our GWAS finding, and the lack of significant GWAS results for polarity at onset also highlight how heterogeneity across cohorts can complicate the analysis of phenotypes and warrant for standardized phenotype definitions.

The coordinated efforts of international consortia and our growing ability to harness the rich phenotypic information stored in electronic health records will provide an unprecedented pool of phenotypic information on an increasingly diverse patient population (Smoller, 2018; Sullivan et al., 2018). Thus, in addition to conducting case-control analyses, studying subphenotypes on a large scale will soon become feasible. However, as the results of the presented two papers also show, sample size is not a silver bullet: analogously to the standardization of diagnostic criteria, careful (sub)phenotype harmonization and coordinated recruitment strategies are also needed so that future studies can benefit from these growing resources.

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2. Paper I

Kalman, J.L., *Papiol, S., Forstner, A.J., [...], Nöthen, M., Rietschel, M., Schulze, T.G. (2018). Investigating polygenic burden in age at disease onset in bipolar disorder: Findings from an international multicentric study. Bipolar Disord, 21(1), 68-75. doi:10.1111/bdi.12659*

Given the large sample size and the complexity of the study and in accordance with the publication practice in the field of genetics, the study has three equally contributing first authors (**J.L.K.,** S.P., and A.J.F.). The contribution of each of the equally contributing coauthor is listed below. The contribution of Janos L. Kalman (J.L.K.) is highlighted.

The study was conducted under the supervision of T.G.S. and S.P (shared first author). The research was designed by **J.L.K.** in consultation with S.P. and A.J.F. **J.L.K.** reached out to the PIs of the individual cohorts, coordinated the transfer of the phenotype and genetic data, performed the quality control of the acquired data, performed the statistical analysis, wrote the manuscript, and accompanied the publication process as corresponding author. S.P. supported **J.L.K.** in the calculation of polygenic risk scores. All co-authors critically revised and approved the manuscript.

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ORIGINAL ARTICLE

WILEY BIPOLAR DISORDERS

Investigating polygenic burden in age at disease onset in bipolar disorder: Findings from an international multicentric study

Janos L Kalman[1,2,3,*] | Sergi Papiol[1,2,4] | Andreas J Forstner[5,6,7] | Urs Heilbronner[1,8] | Franziska Degenhardt[5] | Jana Strohmaier[9] | Mazda Adli[10] | Kristina Adorjan[1,2] | Nirmala Akula[11] | Martin Alda[12] | Heike Anderson-Schmidt[1,8] | Till FM Andlauer[13] | Ion-George Anghelescu[14] | Raffaella Ardau[15] | Bárbara Arias[16] | Volker Arolt[17] | Jean-Michel Aubry[18] | Lena Backlund[19] | Kim Bartholdi[1] | Michael Bauer[20] | Bernhard T Baune[21] | Thomas Becker[22] | Frank Bellivier[23] | Antonio Benabarre[24] | Susanne Bengesser[25] | Abesh Kumar Bhattacharjee[26] | Joanna M Biernacka[27] | Armin Birner[25] | Clara Brichant-Petitjean[23] | Monika Budde[1] | Pablo Cervantes[28] | Caterina Chillotti[15] | Sven Cichon[5,7] | Scott R Clark[21] | Francesc Colom[29] | Ashley L Comes[1,3] | Cristiana Cruceanu[13,28] | Piotr M Czerski[30] | Udo Dannlowski[17] | Alexandre Dayer[18] | Maria Del Zompo[31] | Jay Raymond DePaulo[32] | Detlef E Dietrich[33] | Bruno Étain[23] | Thomas Ethofer[34] | Peter Falkai[2] | Andreas Fallgatter[34] | Christian Figge[35] | Laura Flatau[1] | Here Folkerts[36] | Louise Frisen[19] | Mark A Frye[27] | Janice M Fullerton[37,38] | Katrin Gade[1,8] | Sébastien Gard[39] | Julie S Garnham[12] | Fernando S Goes[32] | Maria Grigoroiu-Serbanescu[40] | Anna Gryaznova[1] | Maria Hake[1] | Joanna Hauser[30] | Stefan Herms[5,7] | Per Hoffmann[5,7] | Liping Hou[11] | Markus Jäger[22] | Stephane Jamain[41] | Esther Jiménez[24] | Georg Juckel[42] | Jean-Pierre Kahn[43] | Layla Kassem[44] | John Kelsoe[26] | Sarah Kittel-Schneider[45] | Sebastian Kliwicki[46] | Farah Klohn-Sagatholislam[1,2] | Manfred Koller[47] | Barbara König[48] | Carsten Konrad[49] | Nina Lackner[25] | Gonzalo Laje[11] | Mikael Landén[50,51] | Fabian U Lang[22] | Catharina Lavebratt[39] | Marion Leboyer[41,52] | Susan G Leckband[53] | Mario Maj[54] | Mirko Manchia[55,56] | Lina Martinsson[57] | Michael J McCarthy[26] | Susan L McElroy[58] | Francis J McMahon[11] | Philip B Mitchell[59,60] | Marina Mitjans[61] | Francis M Mondimore[32] | Palmiero Monteleone[54,62] | Vanessa Nieratschker[34] | Caroline M Nievergelt[26] | Tomas Novák[63,64] | Urban Ösby[65] | Andrea Pfennig[20] | James B Potash[66] |

Janos L. Kalman, Sergi Papiol, Andreas J. Forstner, Markus Nöthen, Marcella Rietschel and Thomas G. Schulze contributed equally to this study.

Daniela Reich-Erkelenz[1] | Andreas Reif[45] | Jens Reimer[67] | Eva Reininghaus[25] | Markus Reitt[8] | Stephan Ripke[10,68] | Guy A Rouleau[28] | Janusz K Rybakowski[46] | Martin Schalling[19] | Harald Scherk[69] | Max Schmauß[70] | Peter R Schofield[37,38] | K Oliver Schubert[21] | Eva C Schulte[1,2] | Sybille Schulz[67] | Fanny Senner[1,2] | Giovanni Severino[31] | Tatyana Shekhtman[26] | Paul D Shilling[26] | Christian Simhandl[71,72] | Claire M Slaney[12] | Carsten Spitzer[73] | Alessio Squassina[31] | Thomas Stamm[10,74] | Sophia Stegmaier[34] | Sebastian Stierl[75] | Pavla Stopkova[63] | Andreas Thiel[49] | Sarah K Tighe[66] | Alfonso Tortorella[76] | Gustavo Turecki[77] | Eduard Vieta[24] | Julia Veeh[45] | Martin von Hagen[78] | Moritz E Wigand[22] | Jens Wiltfang[8] | Stephanie Witt[9] | Adam Wright[59,60] | Peter P Zandi[32] | Jörg Zimmermann[67] | Markus Nöthen[5] | Marcella Rietschel[9] | Thomas G Schulze[1]

[1]Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Munich, Germany

[2]Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-University Munich, Munich, Germany

[3]International Max Planck Research School for Translational Psychiatry (IMPRS-TP), Munich, Germany

[4]Instituto de Salud Carlos III, Biomedical Network Research Centre on Mental Health (CIBERSAM), Barcelona, Spain

[5]Institute of Human Genetics, University of Bonn and Department of Genomics, Life & Brain Center, Bonn, Germany

[6]Department of Psychiatry (UPK), University of Basel, Basel, Switzerland

[7]Human Genomics Research Group, Department of Biomedicine, University of Basel, Basel, Switzerland

[8]Department of Psychiatry and Psychotherapy, University Medical Center (UMG), Georg-August University Göttingen, Göttingen, Germany

[9]Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany

[10]Department of Psychiatry and Psychotherapy, Charité - Universitätsmedizin Berlin, Berlin, Germany

[11]Intramural Research Program, National Institute of Mental Health, National Institutes of Health, US Dept of Health & Human Services, Bethesda, MD, USA

[12]Department of Psychiatry, Dalhousie University, Halifax, NS, Canada

[13]Max Planck Institute of Psychiatry, Munich, Germany

[14]Private Neuropathic Hospital Dr. med. Kurt Fontheim, Liebenburg, Germany

[15]Unit of Clinical Pharmacology, Hospital University Agency of Cagliari, Cagliari, Italy

[16]Departament Biologia Evolutiva, Ecologia i Ciències Ambientals, Facultat de Biologia, Institut de Biomedicina de la Universitat de Barcelona (IBUB), CIBERSAM, Universitat de Barcelona, Barcelona, Spain

[17]Department of Psychiatry, University of Münster, Münster, Germany

[18]Mood Disorders Unit, Department of Psychiatry, HUG - Geneva University Hospitals, Geneva, Switzerland

[19]Department of Molecular Medicine and Surgery, Karolinska Institutet and The Centre for Psychiatric Research, Stockholm, Sweden

[20]Department of Psychiatry and Psychotherapy, Carl Gustav Carus University Hospital, Technische Universität Dresden, Dresden, Germany

[21]Discipline of Psychiatry, Royal Adelaide Hospital, Adelaide School of Medical Schooline, The University of Adelaide, Adelaide, SA, Australia

[22]Department of Psychiatry II, Ulm University, Bezirkskrankenhaus Günzburg, Günzburg, Germany

[23]INSERM UMR-S 1144 - Université Paris Diderot, Pôle de Psychiatrie, AP-HP, Groupe Hospitalier Lariboisière-F. Widal, Paris, France

[24]Bipolar Disorders Program, Institute of Neurosciences, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Spain

[25]Medical University of Graz, Graz, Austria

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

[27]Mayo Clinic, Rochester, MN, USA

[28]Mood Disorders Program, McGill University Health Centre, Montreal, QC, Canada

[29]Mental Health Program, IMIM (Hospital del Mar Medical Research Institute), CIBERSAM Barcelona, Catolonia, Spain

[30]Laboratory of Psychiatric Genetics, Poznan University of Medical Sciences, Poznan, Poland

[31]Department of Biomedical Sciences, University of Cagliari, Cagliari, Italy

[32]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, Baltimore, MD, USA

[33]AMEOS Clinical Center Hildesheim, Hildesheim, Germany

[34]Department of Psychiatry and Psychotherapy, Neurophysiology & Interventional Neuropsychiatry, University of Tübingen, Tübingen, Germany

[35]Karl-Jaspers Clinic, European Medical School Oldenburg-Groningen, Oldenburg, Germany

[36]Department of Psychiatry, Psychotherapy and Psychosomatics, Clinical Center Wilhelmshaven, Wilhelmshaven, Germany

[37]Neuroscience Research Australia, Sydney, NSW, Australia

[38]School of Medical Sciences, University of New South Wales, Sydney, NSW, Australia

[39]CH Ch Perrens, Bordeaux, France

[40]Biometric Psychiatric Genetics Research Unit, Alexandru Obregia Clinical Psychiatric Hospital, Bucharest, Romania

[41]INSERM U955 Equipe 15 - Psychiatrie Genetique, Hopital Henri Mondor, Creteil, Cedex, France

[42]Department of Psychiatry, Ruhr University Bochum, LWL University Hospital, Bochum, Germany

[43]Service de Psychiatrie et Psychologie Clinique, Centre Psychothérapique de Nancy - Université de Lorraine, Nancy, France

[44]Human Genetics Branch, Section on Genetic Basis of Mood and Anxiety Disorders, National Institutes of Health, Bethesda, MD, USA

[45]Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt, Frankfurt, Germany

[46]Department of Adult Psychiatry, Poznan University of Medical Sciences, Poznan, Poland

[47]Asklepios Specialized Hospital, Göttingen, Germany

[48]Hospital Neunkirchen, Neunkirchen, Germany

[48]Department of Psychiatry and Psychotherapy, Agaplesion Diakonieklinikum, Rotenburg, Germany

[50]Gothenburg University, Sahlgrenska Academy, Gothenburg, Sweden

[51]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

[52]Assistance Publique-Hôpitaux de Paris, Hôpital Albert Chenevier - Henri Mondor, Pôle de Psychiatrie, Créteil, France

[53]Department of Pharmacy, VA San Diego Healthcare System, San Diego, CA, USA

[54]Department of Psychiatry, Campania University L. Vanvitelli, Naples, Italy

[55]Section of Psychiatry, Department of Public Health, Clinical and Molecular Medicine, University of Cagliari, Cagliari, Italy

[56]Department of Pharmacology, Dalhousie University, Halifax, NS, Canada

[57]Department of Clinical Neurosciences, Karolinska Institutet, Stockholm, Sweden

[58]Lindner Center of HOPE, Research Institute, Mason, OH, USA

[59]School of Psychiatry, University of New South Wales, Sydney, NSW, Australia

[60]Black Dog Institute, Prince of Wales Hospital, Sydney, NSW, Australia

[61]Unitat d'Antropologia (Dp. Biología Animal), Department of Biologia Animal, Facultat de Biologia and Institut de Biomedicina (IBUB), Universitat de Barcelona, CIBERSAM, Barcelona, Spain

[62]Neurosciences Section, Department of Medicine and Surgery, University of Salerno, Salerno, Italy

[63]National Institute of Mental Health, Klecany, Czech Republic

[64]Third Faculty of Medicine, Charles University in Prague, Prague, Czech Republic

[65]Department of Psychiatry, Karolinska Institutet, Stockholm, Sweden

[66]Psychiatry, University of Iowa, Iowa City, IA, USA

[67]Department of Psychiatry, Klinikum Bremen-Ost, Bremen, Germany

[68]Stanley Center for Psychiatric Research, Broad Institute, Cambridge, MA, USA

[69]AMEOS Clinical Center Osnabrück, Osnabrück, Germany

[70]Department of Psychiatry and Psychotherapy, Bezirkskrankenhaus Augsburg, Augsburg, Germany

[71]Sigmund Freud University, Vienna, Austria

[72]Bipolar Zentrum, Wiener Neustadt, Austria

[73]ASKLEPIOS Specialized Hospital Tiefenbrunn, Rosdorf, Germany

[74]Department of Psychiatry, Psychotherapy and Psychosomatics, Medical School Brandenburg, Neuruppin, Germany

[75]Psychiatric Hospital Lüneburg, Lüneburg, Germany

[76]Department of Psychiatry, University of Perugia, Perugia, Italy

[77]Douglas Hospital, Verdun, QC, Canada

[78]Clinic for Psychiatry and Psychotherapy, Clinical Center Werra-Meißner, Eschwege, Germany

Correspondence
Janos L Kalman, Institute of Psychiatric Phenomics and Genomics (IPPG), Medical Center of the University of Munich LMU, Munich, Germany.
Email: janos.kalman@med.uni-muenchen.de

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Objectives: Bipolar disorder (BD) with early disease onset is associated with an unfavorable clinical outcome and constitutes a clinically and biologically homogenous subgroup within the heterogeneous BD spectrum. Previous studies have found an accumulation of early age at onset (AAO) in BD families and have therefore hypothesized that there is a larger genetic contribution to the early-onset cases than to late onset BD. To investigate the genetic background of this subphenotype, we evaluated whether an increased polygenic burden of BD- and schizophrenia (SCZ)-associated risk variants is associated with an earlier AAO in BD patients.

Methods: A total of 1995 BD type 1 patients from the Consortium of Lithium Genetics (ConLiGen), PsyCourse and Bonn-Mannheim samples were genotyped and their BD and SCZ polygenic risk scores (PRSs) were calculated using the summary statistics of the Psychiatric Genomics Consortium as a training data set. AAO was either separated into onset groups of clinical interest (childhood and adolescence [≤18 years] vs adulthood [>18 years]) or considered as a continuous measure. The associations between BD- and SCZ-PRSs and AAO were evaluated with regression models.

Results: BD- and SCZ-PRSs were not significantly associated with age at disease onset. Results remained the same when analyses were stratified by site of recruitment.

Conclusions: The current study is the largest conducted so far to investigate the association between the cumulative BD and SCZ polygenic risk and AAO in BD patients. The reported negative results suggest that such a polygenic influence, if there is any, is not large, and highlight the importance of conducting further, larger scale studies to obtain more information on the genetic architecture of this clinically relevant phenotype.

KEYWORDS
age at onset, bipolar disorder, early onset, polygenic risk score, schizophrenia

1 | INTRODUCTION

Bipolar disorder (BD) is a multifactorial disorder characterized by recurrent episodes of elevated and depressed mood. According to heritability estimates, genetic factors explain 60%-80% of the variance in this disorder and recent association studies have shown that a significant proportion of its genetic liability can be attributed to common variation.[1-4] Despite this relatively robust genetic component, the phenotypic and genetic heterogeneity of this mental disorder has hampered our understanding of the underlying biological mechanisms.[4]

Studies on breast cancer, colon cancer, and Alzheimer's disease have provided evidence that identifying subphenotypes underlying the clinical diagnosis can assist with patient stratification. This approach, of narrowing down the molecular heterogeneity of these complex and polygenic disorders, holds promise for the identification of the genetic factors involved.[5,6] In BD, the presence and severity of psychotic symptoms, first episode polarity, response to lithium, functional impairments, and age at onset (AAO) are considered as promising phenotypes for the identification of putatively biologically homogenous disease-subgroups.[7,8] The recent identification of novel lithium response-associated single nucleotide polymorphisms (SNPs) by the Consortium of Lithium Genetics (ConLiGen) and Song et al. underline the potential of this approach in BD and call for further analyses on similar well-defined subphenotypes.[9,10]

Clinical studies have shown that early-onset BD (onset prior to 18 years of age) is more severe and homogeneous than other forms of BD, and thus it is one of the most frequently examined subphenotype candidates. This subgroup is associated with a higher recurrence rate of mood episodes, higher rates of psychotic symptoms and of comorbid conditions and more frequent suicide attempts and neurocognitive impairments.[8,11] Moreover, it has also been hypothesized, mostly based on the observations of family and heritability studies, that early-onset BD is genetically different from the late-onset subgroup.[12,13] However, candidate gene studies and genome-wide association studies (GWASs) have failed to unambiguously identify genetic markers specifically associated with early-onset forms of BD. This may be in part due to limited statistical power.[14,15]

Current evidence derived from GWASs, in a wide range of psychiatric (and non-psychiatric) complex phenotypes, indicates that the genetic architecture of psychiatric disorders is characterized by a marked polygenicity.[16-18] Therefore, estimating the genetic risk burden by employing polygenic risk scores (PRSs) holds promise for a better understanding of the genetic basis of the phenotype and its genetic overlap with other phenotypes/disorders.[18,19] For instance, genome-wide complex trait analysis has shown that 79% of common variants are shared between BD and schizophrenia (SCZ) and that SCZ-PRSs are good predictors of BD case-control status.[2,18] However, a single study thus far has investigated the association between the cumulative genomic risk for BD (BD-PRS) and disease onset and found no significant results.[20] The association with SCZ-PRS has not been tested yet.

Given the limited knowledge of the genetic structure of AAO in BD, the aim of the current study was to use PRSs to investigate whether earlier disease onset is associated with a higher genetic liability to BD and/or SCZ in 1995 BD type 1 patients.

2 | METHODS

2.1 | Subjects

The phenotypic and genetic data of patients with a lifetime diagnosis of DSM-III or DSM-IV BD type 1 were assembled from the ConLiGen, Bonn-Mannheim (BoMa) and PsyCourse samples. Patients included in this analysis were recruited at 21 sites in 12 countries across North America (Canada and the USA), Europe (Austria, Czech Republic, Italy, France, Germany, Poland, Romania, Spain and Sweden) and Australia. Their AAO was defined as the age at the first DSM-III or DSM-IV mood episode (depressive, manic or hypomanic) based on the information obtained at the diagnostic interview and from medical records. Ascertainment and diagnostic assessment for the ConLiGen study have been described previously.[7,9] Patients in the BoMa sample were recruited from consecutive hospital admissions at the Central Institute of Mental Health, Mannheim, and the Department of Psychiatry, University of Bonn, Bonn, Germany.[21] Only patients not part of the PGC-BD1 analyses were included in the current study.[22] PsyCourse is an ongoing, multicenter study conducted at a network of clinical sites across Germany and Austria (http://psycourse.de).[23] The phenotypic characteristics of the patients recruited at the individual sites and the respective sample sizes are presented in Supporting Information Table S1. The reported sample sizes represent those available after quality control (exclusion of patients with no information on age [N = 59], gender [N = 2], or AAO, or having improbable AAO data [N = 162]).

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all participants aged ≥ 18 years, and written assent and parental permission were obtained from children aged < 18 years and their parent/legal guardian before participation in the study. Approval from each institution's ethics committees was obtained.

2.2 | Genotyping and imputation

DNA was extracted from peripheral blood and samples were genotyped at the National Institute of Mental Health (Bethesda, MD, USA) or Broad Institute (ConLiGen) and Life & Brain Center at the University of Bonn (ConLiGen, PsyCourse and BoMa). The genotyping, quality control and imputation pipelines used for the samples are described in Hou et al., Andlauer et al. and Mühlheisen et al. in more detail.[9,21,24] Briefly, the subsamples were genotyped on Affymetrix (Affymetrix 6.0, Affymetrix Inc., Santa Clara, CA, USA) or Illumina (Human610/660W, HumanOmniExpress, HumanOmni1-Quad or HumanOmni2.5, Illumina Inc., San Diego, CA, USA) SNP arrays. Participants from the PsyCourse and BoMa cohorts were genotyped on Illumina (Human610/660W or Infinium PsychArray) SNP arrays. Quality control and imputation were carried out separately for the distinct SNP arrays. Genotype imputation was performed using the 1000 Genomes reference panel using either SHAPEIT2 and IMPUTE2 (BoMa and PsyCourse) or SHAPEIT2 and minimac (ConLiGen).[25,26] The Caucasian-European origin of the samples was confirmed by principal component analysis of the genetic relationship matrix.

2.3 | Polygenic scoring

Polygenic scores were generated using PLINK v.1.9, by applying the method used by the International Schizophrenia Consortium, as described in Purcell et al.[18,27] First, the SNPs shared between either

the Psychiatric Genomics Consortiums SCZ or BD GWAS summary statistics data sets (PGC SCZ2 and PGC BD) and a merged data set of the samples included in this study were identified, resulting in N = 92 703 (SCZ) and N = 101 007 (BD) autosomal SNPs pruned for minimalizing pair-wise linkage disequilibrium.[17,22] This harmonized set of PGC SCZ2 and PGC BD summary data was then used as the source of information on the allelic risk variants and their associated odds ratios (ORs). PRSs were calculated by multiplying the imputation probability for each risk allele by the log(OR) for each genetic variant in PGC SCZ2 and PGC BD. The resulting values were summed using all SNPs (*P*-value threshold, $P_T = 1$), leading to an estimate of the SCZ or BD polygenic risk burden of each individual.

2.4 | Statistical analysis

AAO was analyzed both as a continuous and as a categorical measure; the association between AAO and either BD- or SCZ-PRS was evaluated using linear and logistic regression models, respectively. The AAO subgroups were initially identified to represent the developmental stages, namely childhood (≤12 years), adolescence (13-18 years), or adulthood (>18 years).[28] However, because of highly unbalanced sample sizes (N = 93, 555 and 1347, respectively), the childhood and adolescence groups were collapsed into a single early-onset group (≤18 years) and compared to the late-onset cases (>18 years) in the categorical analysis. Sex, age at interview, recruitment site, genotyping chip, 10 ancestry principal components and the applied imputation strategy were taken into consideration as covariates. Backward stepwise regression model selection indicated that the 1st, 4th, 6th and 8th ancestry principal components, site, genotyping chip, age at interview and imputation strategy were significantly associated with the continuous AAO. The 4th, 6th, 7th and 10th ancestry principal components, gender, site, genotyping chip, age at interview and imputation strategy were associated with the categorical AAO measure. Therefore, these variables were controlled for in the respective analyses. The proportion of variance explained (R^2) was calculated by subtracting the effects of the covariates from the full model including PRS. The residuals of the linear regression models were normally distributed. The significance threshold was corrected for testing two PRSs to $\alpha = 0.025$. All analyses were performed in the statistical computing environment R 3.4.2 with the packages car 2.1-5, fmsb 0.6.1 and nnet 7.3-12.[29]

3 | RESULTS

We analyzed a sample of 1995 BD type 1 patients (55.1% female). The mean (± SD) AAO across all centers was 24.83 (±10.59) years and the AAO ranged between 6 and 67 years. The AAO was not different between the sexes (mean ± SD: male patients, 24.96 ± 10.720 years; female patients, 24.73 ± 10.32 years; $P = .623$).

No significant association was observed between continuous AAO and BD-PRS ($P = .376$, $t = -0.886$, standardized $\beta = -0.000065$, R^2 change = −.01%) or SCZ-PRS ($P = .99$, $t = -0.01$, standardized $\beta = -1.322 \times 10^{-6}$, R^2 change = −.04%). Full results, including *P*-values, *t* values and R^2 change are summarized in Supporting Information Tables S2-S3.

Furthermore, no significant group difference was observed when AAO was considered as a dichotomous variable and BD- and SCZ-PRSs of the early-onset (≤18 years) and late-onset (>18 years) AAO groups were compared using binary logistic regression ($P = .16$, Nagelkerke's R^2 change = .105%, OR = 1.01, 95% confidence interval (CI): 0.99-1.03, and $P = .88$, Nagelkerke's R^2 change = .002%, OR = 1.0, 95% CI: 0.96-1.03, respectively). Full results, including correlation coefficients, ORs, 95% CIs and *P*-values, are summarized in Supporting Information Tables S4-S5.

Patients recruited in the USA had a significantly lower AAO compared to those from the European, Australian and Canadian sites (mean ± SD: 19.25 ± 9.55 and 25.92 ± 10.33 years, respectively, $P < 2.25 \times 10^{-26}$). To ensure that the association between AAO and BD- and SCZ-PRSs was not masked by these geographic differences in AAO distribution, which are well known in the literature, the same linear regressions with initial backward feature selection steps were repeated using only the USA site or the other sites. These additional analyses, similarly to the results for the full data set, found no association with the phenotype of interest. Full results, including *P*-values, *t* values and R^2 change, are summarized in Supporting Information Tables S6-S9.

4 | DISCUSSION

Although early onset of BD has long been hypothesized to constitute a genetically more homogenous subcategory within the rather heterogenous BD spectrum, the search for phenotype-specific genetic variants has not yet been successful.[12] Being a highly heritable disorder with 43.2% of its genetic liability being explained by common variants of small effect, the development of BD, similarly to that of other complex polygenic conditions, can be modeled within the framework of a liability-threshold model.[2] Individuals with more BD- or SCZ-associated risk alleles can be expected to cross the liability threshold earlier and thus have an earlier disease onset.[30] Previous family studies support this hypothesis, as affected siblings of patients with early AAO were reported to be four times more likely to also have an early AAO, and children of couples with a positive history of affective disorders had a higher risk for an earlier AAO.[31,32] However, a study conducted on 255 patients found no difference between the BD-PRSs of the different AAO groups.[20]

Evidence shows that the power to detect the genetic underpinnings of complex phenotypes increases with increasing sample sizes. Therefore, we assumed that, using an order of magnitude larger sample than in Aminoff et al., we might find an association between AAO and BD and SCZ.[20] Based on the negative findings of our study, one can hypothesize that instead of being largely influenced by SNPs identified in GWASs of BD and SCZ, age at disease onset is rather influenced by other genetic, environmental or epigenetic risk factors. A further possibility is that BD- and SCZ-PRSs explain only a small proportion of the AAO variance and/or the genetics of AAO in BD is more heterogenous

than previously assumed and therefore the current study lacked the statistical power to detect an underlying association.

5 | SUMMARY

To our knowledge, this is the largest study thus far to investigate the association between AAO in BD and BD- and SCZ-PRS. The results show, in our sample of 1995 BD patients, that the polygenic burden associated with BD or SCZ risk does not influence the age at illness onset in BD. These negative results highlight the need to conduct further larger scale studies, also including environmental information, to disentangle the genetic architecture of early-onset BD.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest. The funding agencies had no role in the design of the study; in the collection, analyses, or interpretation of data. Neither were they involved in the writing of the manuscript, or in the decision to publish the results.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Investigating polygenic burden in age at disease onset in bipolar disorder - Findings from an international multicentric study

Supplementary Material

Centre	N (male)	Age (mean ±SD, range)	Age at onset (mean ±SD, range)	Early Age at Onset (%)	BD-PRS (mean ±SD)	SCZ-PRS (mean ±SD)
Whole dataset	1995 (44.91%)	46.22 (±13.76, 12-89)	24.83 (±10.59, 6-67)	32.48%	35.85 (±6,01)	-15.11 (±3.23)
ConLiGen						
University of Adelaide, Adelaide (Australia)	59 (44.1%)	52.81 (±12.64, 30-83)	27.68 (±10.60, 13-64)	25.4%	38.22 (±6.22)	-14.42 (±3.91)
University of Barcelona, Barcelona (Catalonia)	57 (42.1%)	42.82 (±11.25, 23-68)	25.96 (±9.43, 13-49)	26.3%	37.59 (±5.92)	-14.20 (±2.95)
University of Cagliari, Cagliari (Italy)	146 (34.2%)	43.32 (±14.26, 18-82)	25.82 (±10.17, 13-67)	24.7%	36.38 (±5.34)	-15.25 (±2.58)
Technical University Dresden, Dresden (Germany)	24 (41.7%)	42.96 (±12.96, 23-70)	24.50 (±8.30, 13-44)	25.0%	36.84 (±8.18)	-15.23 (±3.98)
University of Graz, Graz (Austria)	35 (54.3%)	50.37 (±16.33, 21-82)	27.23 (±12.44, 13-59)	31.4%	36.31 (±5.51)	-13.88 (±2.72)
Dalhousie University, Halifax (Canada)	220 (44.5%)	48.37 (±13.44, 19-82)	24.95 (±9.12, 7-56)	29.1%	36.53 (±5.73)	-15.25 (±3.00)
Johns Hopkins University, Baltimore (USA)	37 (32.4%)	42.59 (±11.72, 12-66)	22.89 (±9.61, 6-49)	29.7%	41.23 (±6.81)	-14.96 (±3.36)
University of Iowa. Iowa City (USA)	25 (44.0%)	45.28 (±14.75, 19-73)	19.52 (±9.73, 6-47)	60.0%	38.09 (±7.97)	-14.88 (±3.74)
University of Napoli, Napoli (Italy)	38 (52.6%)	46.45 (±11.53, 21-73)	27.89 (±9.26, 18-53)	10.5%	34.93 (±5.04)	-11.53 (±2.86)
Mayo Clinic, Rochester (USA)	42 (40.5%)	51.36 (±15.54, 23-75)	23.10 (±11.95, 10-55	50.0%	35.91 (±5.63)	-14.50 (±3.59)
National Institute of Mental Health, Bethesda (USA)	30 (20.0%)	44.7 (±13.04, 21-69)	20.13 (±6.40, 10-36)	46.7%	39.71 (±9.05)	-15.26 (±3.04)
INSERM, Paris (France)	162 (41.4%)	43.84 (±12.10, 19-75)	24.69 (±9.46, 11-56)	29.6%	36.53 (±5.26)	-15.28 (±2.71)
Poznan University of Medical Sciences, Poznan (Poland)	58 (39.7%)	62.40 (±10.64, 35-89)	32.24 (±10.63, 18-55)	5.2%	32.81 (±4.82)	-14.61 (±2.62)

Prague Psychiatric Center, Prague (Czech Republic)	38 (36.8%)	42.92 (±14.07, 24-80)	27.87 (±10.10, 16-52)	10.5%	34.81 (±5.68)	-13.72 (±3.13)
Obregia Hospital, Bucharest (Romania)	152 (48.7%)	44.05 (±11.96, 17-73)	25.53 (±8.97, 13-59)	24.3%	33.00 (±5.44)	-13.05 (±3.00)
University of California, San Diego (USA)	192 (54.7%)	45.32 (±12.68, 17-79)	17.54 (±8.96, 6-66)	69.3%	37.23 (±6.76)	-15.79 (±3.12)
Karolinska Institutet, Stockholm (Sweden)	232 (43.1%)	45.29 (±14.92, 18-82)	23.26 (±9.29, 7-56)	39.7%	34.82 (±5.40)	-15.52 (±3.09)
University of NSW, Sydney (Australia)	23 (47.8%)	44.00 (±15.71, 22-69)	22.61 (±9.65, 11-56)	47.8%	36.22 (±5.68)	-15.00 (±4.83)
University of Würzburg, Würzburg (Germany)	48 (47.9%)	52.85 (±13.97, 25-78)	29.56 (±11.73, 15-58)	18.8%	37.27 (±5.18)	-15.09 (±3.42)
Bonn-Mannheim sample (Germany)						
Central Institute of Mental Health, Mannheim, and the Department of Psychiatry, University of Bonn, Bonn (Germany)	186 (47.3%)	44.37 (±13.00, 17-73)	26.90 (±12.15, 8-63)	28.8%	34.87 (±5.30)	-15.92 (±3.03)
PsyCourse sample (Germany)						
PsyCourse study (Germany/Austria)	191 (51.3%)	46.39 (±13.35, 18-76)	26.89 (±11.36, 9-61)	24.6%	34.64 (±5.89)	-16.32 (±3.29)

Supplementary table 2.: Full results (standardized correlation coefficient, t-value and p-value) for the linear regression on age at onset and BD-PRS. Variables, found to be associated with age at onset using backward regression were included as covariates. (p=0.376, t=-0.886, standardized beta=-0.000065, R^2 change=-0.01%)

	Standardized correlation coefficient	t-value	p-value
(Intercept)		3.06	0.00
Age at interview	0.47	23.82	0.00
Centre 2: Barcelona (Catalonia)	1.89	1.74	0.08
Centre 3: Cagliari (Italy)	0.38	0.33	0.74
Centre 4: Halifax (Canada)	-0.29	-2.20	0.03
Centre 5: Dresden (Germany)	0.00	-0.40	0.69
Centre 6: Graz (Austria)	-0.01	-0.68	0.50
Centre 7: Baltimore (USA)	-0.01	-0.67	0.51
Centre 8: Iowa City (USA)	-0.02	-1.76	0.08
Centre 9: Napoli (Italy)	2.53	2.05	0.04
Centre 10: PsyCourse study (Germany/Austria)	-2.97	-0.55	0.58
Centre 11: Rochester (USA)	-4.80	-1.57	0.12
Centre 12: Bethesda (USA)	-1.89	-1.76	0.08
Centre 13: Paris (France)	0.11	0.70	0.49
Centre 14: Poznan (Poland)	-0.01	-0.64	0.52
Centre 15: Prague (Czech Republic)	0.00	0.00	1.00
Centre 16: Bucharest (Romania)	-0.01	-1.61	0.11
Centre 17: San Diego (USA)	-0.02	-2.47	0.01
Centre 18: Stockholm (Sweden)	-3.96	-1.31	0.19
Centre 19: Sydney (Australia)	-7.56	-1.10	0.27
Centre 20: Würzburg (Germany)	1.25	1.21	0.23
Centre 21: Mannheim/Bonn (Germany)	-0.33	-0.32	0.75
Chip 2: Illumina Human610	-0.13	-0.39	0.70
Chip 3: Illumina Human 660W	-0.02	-1.57	0.12
Chip 5: Illumina HumanOmniExpress 1.0	-0.01	-2.40	0.02
Chip 7: Affymetrix 6.0	-0.01	-2.14	0.03
Chip 8: Illumina HumanOmni1-Quad	0.00	-0.06	0.95
Chip 9: Illumina HumanOmniExpress 1.1	-4.80	-1.55	0.12
Imputation 2. wave	5.89	1.37	0.17
PC1	27.63	1.83	0.07
PC4	-4.44	-2.00	0.05
PC6	1.43	1.88	0.06
PC8	0.05	2.30	0.02
BD-PRS at pT=1	**0.00**	**-0.89**	**0.38**

Supplementary table 3.: Full results (standardized correlation coefficient, t-value and p-value) for the linear regression on age at onset and SCZ-PRS. Variables, found to be associated with age at onset using backward regression were included as covariates. (p=0.99, t=-0.01, standardized beta= 0.00, R^2 change=-0.04%)

	Standardized correlation coefficient	t-value	p-value
(Intercept)		2.85	0.00
Age at interview	0.47	23.77	0.00
Centre 2: Barcelona (Catalonia)	1.87	1.73	0.08
Centre 3: Cagliari (Italy)	0.11	0.28	0.78
Centre 4: Halifax (Canada)	-0.86	-2.20	0.03
Centre 5: Dresden (Germany)	0.00	-0.45	0.66
Centre 6: Graz (Austria)	-0.01	-0.71	0.48
Centre 7: Baltimore (USA)	-0.01	-0.73	0.47
Centre 8: Iowa City (USA)	-0.02	-1.81	0.07
Centre 9: Napoli (Italy)	1.37	2.07	0.04
Centre 10: PsyCourse study (Germany/Austria)	-3.08	-0.57	0.57
Centre 11: Rochester (USA)	-4.89	-1.60	0.11
Centre 12: Bethesda (USA)	-0.66	-1.81	0.07
Centre 13: Paris (France)	0.32	0.68	0.49
Centre 14: Poznan (Poland)	-0.01	-0.64	0.52
Centre 15: Prague (Czech Republic)	0.00	-0.02	0.99
Centre 16: Bucharest (Romania)	-0.01	-1.64	0.10
Centre 17: San Diego (USA)	-0.02	-2.50	0.01
Centre 18: Stockholm (Sweden)	-2.18	-1.34	0.18
Centre 19: Sydney (Australia)	-7.78	-1.13	0.26
Centre 20: Würzburg (Germany)	1.27	1.23	0.22
Centre 21: Mannheim/Bonn (Germany)	-0.12	-0.35	0.73
Imputation 2. wave	1.17	1.43	0.15
Chip 2: Illumina Human610	0.00	-0.36	0.72
Chip 3: Illumina Human 660W	-0.02	-1.63	0.10
Chip 5: Illumina HumanOmniExpress 1.0	-0.01	-2.51	0.01
Chip 7: Affymetrix 6.0	-0.01	-2.23	0.03
Chip 8: Illumina HumanOmni1-Quad	-0.11	-0.10	0.92
Chip 9: Illumina HumanOmniExpress 1.1	-11.50	-1.62	0.11
PC1	26.86	1.77	0.08
PC4	-1.47	-1.94	0.05
PC6	4.10	1.85	0.06
PC8	0.05	2.29	0.02
SCZ-PRS at pT=1	**0.00**	**-0.01**	**0.99**

Supplementary table 4.: Full results (correlation coefficient, OR, 95% CI and p-value) for the binary logistic regression comparing the BD-PRS of the early-onset (≤18 years) vs. late-onset (>18 years) AAO groups. Variables, found to be associated with the age at onset groups using backward regression were included as covariates. (p=0.16, Nagelkerke´s R2 change: 0.105%; OR=1.01 (95% CI: 0.99-1.03)).

	Correlation coefficient	OR	CI (95%)	p-value
(Intercept)	-14.52	$4.97x10^{7}$	$2.24x10^{-261}$ - $1.1x10^{248}$	0.96
Age at interview	-0.06	0.94	0.93 - 0.95	$1.27x10^{-37}$
Gender	0.20	1.23	0.98 - 1.52	0.06
Centre 2: Barcelona (Catalonia)	-0.51	0.60	0.25 - 1.42	0.25
Centre 3: Cagliari (Italy)	15.41	$4.94x10^{6}$	$2.22x10^{-248}$ - $1.09x10^{261}$	0.96
Centre 4: Halifax (Canada)	0.55	1.73	0.78 - 3.82	0.18
Centre 5: Dresden (Germany)	14.25	$1.54x10^{6}$	$6.91x10^{-249}$ - $3.41x10^{260}$	0.96
Centre 6: Graz (Austria)	16.26	$1.16x10^{7}$	$5.20x10^{-248}$ - $2.56x10^{261}$	0.96
Centre 7: Baltimore (USA)	15.01	$3.30x10^{6}$	$1.48x10^{-248}$ - $7.30x10^{260}$	0.96
Centre 8: Iowa City (USA)	17.33	$3.35x10^{7}$	$1.50x10^{-247}$ - $7.42x10^{261}$	0.95
Centre 9: Napoli (Italy)	-1.61	0.19	0.05 - 0.69	0.01
Centre 10: PsyCourse study (Germany/Austria)	15.33	$4.54x10^{6}$	$2.05x10^{-248}$ - $1.00x10^{261}$	0.96
Centre 11: Rochester (USA)	17.19	$2.93x10^{7}$	$1.31x10^{-247}$ - $6.49x10^{261}$	0.95
Centre 12: Bethesda (USA)	16.07	$9.53x10^{6}$	$4.30x10^{-248}$ - $2.11x10^{261}$	0.96
Centre 13: Paris (France)	-0.10	0.90	0.34 - 2.34	0.84
Centre 14: Poznan (Poland)	14.55	$2.08x10^{6}$	$9.35x10^{-249}$ - $4.60x10^{260}$	0.96
Centre 15: Prague (Czech Republic)	14.12	$1.36x10^{6}$	$6.12x10^{-249}$ - $3.01x10^{260}$	0.96
Centre 16: Bucharest (Romania)	2.52	12.4	1.69 - 90.40	0.01
Centre 17: San Diego (USA)	17.13	$2.74x10^{7}$	$1.23x10^{-247}$ - $6.06x10^{261}$	0.95
Centre 18: Stockholm (Sweden)	17.06	$2.58x10^{7}$	$1.16x10^{-247}$ - $5.71x10^{261}$	0.95
Centre 19: Sydney (Australia)	16.71	$1.81x10^{7}$	$8.13x10^{-248}$ - $4.00x10^{261}$	0.96
Centre 20: Würzburg (Germany)	-0.36	0.7	0.26 - 1.85	0.47
Centre 21: Mannheim/Bonn (Germany)	15.23	$4.13x10^{6}$	$1.86x10^{-248}$ - $9.15x10^{260}$	0.96
Chip 2: Illumina Human610	1.19	3.29	0.28 - 38.10	0.34
Chip 3: Illumina Human 660W	17.40	$3.61x10^{7}$	$1.62x10^{-247}$ - $8.03x10^{261}$	0.95
Chip 5: Illumina HumanOmniExpress 1.0	1.54	4.68	1.91 - 11.5	0.00
Chip 7: Affymetrix 6.0	0.66	1.93	1.04 - 3.59	0.04
Chip 8: Illumina HumanOmni1-Quad	14.75	$2.54x10^{6}$	$1.15x10^{-248}$ - $5.63x10^{260}$	0.96
Chip 9: Illumina HumanOmniExpress 1.1	17.64	$4.60x10^{7}$	$2.07x10^{-247}$ - $1.02x10^{262}$	0.95
Imputation: wave 2	-1.93	0.15	0.03 - 0.82	0.03
PC4	12.15	$1.90x10^{5}$	6.16 - $5.85x10^{9}$	0.02
PC6	-7.81	0.00	$2.77x10^{-8}$ - 5.91	0.11

PC7	-6.63	0.00	$2.24x10^{-7}$ - 7.81	0.13
PC10	-9.67	$6.29x10^{-5}$	$2.91x10^{-8}$ - 0.13	0.01
BD-PRS at pT=1	**0.01**	**1.01**	**0.99 - 1.03**	**0.16**

Supplementary table 5.: Full results (correlation coefficient, OR, 95% CI and p-value) for the binary logistic regression comparing the SCZ-PRS of the early-onset (≤18 years) vs. late-onset (>18 years) AAO groups. Variables, found to be associated with the age at onset groups using backward regression were included as covariates. (p=0.88, Nagelkerke´s R2 change: 0.002%; OR=1.0 (95% CI: 0.96-1.03)).

	Correlation coefficient	OR	CI (95%)	p-value
(Intercept)	-14.14	$7.20x10^{-7}$	$4.79x10^{-261}$ - $1.08x10^{248}$	0.96
Age at interview	-0.06	0.94	0.936 - 0.953	2.26E-37
Gender	0.21	1.23	0.989 - 1.53	0.06
Centre 2: Barcelona (Catalonia)	-0.52	0.60	0.25 - 1.42	0.24
Centre 3: Cagliari (Italy)	15.47	$5.26x10^{6}$	$3.5x10^{-248}$ - $7.9x10^{260}$	0.96
Centre 4: Halifax (Canada)	0.54	1.72	0.778 - 3.8	0.18
Centre 5: Dresden (Germany)	14.34	$1.68x10^{6}$	$1.12x10^{-248}$ - $2.54x10^{+260}$	0.96
Centre 6: Graz (Austria)	16.34	$1.24x10^{7}$	$8.25x10^{-248}$ - $1.87x10^{261}$	0.96
Centre 7: Baltimore (USA)	15.12	$3.69x10^{6}$	$2.46x10^{-248}$ - $5.55x10^{260}$	0.96
Centre 8: Iowa City (USA)	17.42	$3.68x10^{7}$	$2.44x10^{-247}$ - $5.55x10^{261}$	0.95
Centre 9: Napoli (Italy)	-1.63	0.20	0.0563 - 0.685	0.01
Centre 10: PsyCourse study (Germany/Austria)	15.36	$4.71x10^{6}$	$3.13x10^{-248}$ - $7.08x10^{260}$	0.96
Centre 11: Rochester (USA)	17.26	$3.13x10^{7}$	$2.07x10^{-247}$ - $4.71x10^{261}$	0.95
Centre 12: Bethesda (USA)	16.17	$1.05x10^{7}$	$6.97x10^{-248}$ - $1.58x10^{261}$	0.96
Centre 13: Paris (France)	-0.09	0.91	0.35 - 2.36	0.85
Centre 14: Poznan (Poland)	14.55	$2.08x10^{6}$	$1.38x10^{-248}$ - $3.14x10^{260}$	0.96
Centre 15: Prague (Czech Republic)	14.16	$1.42x10^{6}$	$9.43x10^{-249}$ - $2.13x10^{260}$	0.96
Centre 16: Bucharest (Romania)	2.56	12.9	1.77 - 94.2	0.01
Centre 17: San Diego (USA)	17.18	$2.89x10^{7}$	$1.92x10^{-247}$ - $4.34x10^{261}$	0.95
Centre 18: Stockholm (Sweden)	17.14	$2.78x10^{7}$	$1.85x10^{-247}$ - $4.19x10^{261}$	0.95
Centre 19: Sydney (Australia)	16.78	$1.94x10^{7}$	$1.29x10^{-247}$ - $2.93x10^{261}$	0.96
Centre 20: Würzburg (Germany)	-0.37	0.69	0.26 - 1.84	0.46
Centre 21: Mannheim/Bonn (Germany)	15.28	$4.31x10^{6}$	$2.87x10^{-248}$ - $6.48x10^{260}$	0.96
Chip 2: Illumina Human610	1.15	3.14	0.26 - 36.8	0.36
Chip 3: Illumina Human 660W	17.53	$4.12x10^{7}$	$2.73x10^{-247}$ - $6.21x10^{261}$	0.95
Chip 5: Illumina HumanOmniExpress 1.0	1.61	5.02	2.05 - 12.3	0.00
Chip 7: Affymetrix 6.0	0.70	2	1.08 - 3.72	0.03
Chip 8: Illumina HumanOmni1-Quad	14.81	$2.71x10^{6}$	$1.8x10^{-248}$ - $4.06x10^{260}$	0.96

Chip 9: Illumina HumanOmniExpress 1.1	17.81	$5.42x10^{7}$	$3.6x10^{-247}$ - $8.17x10^{261}$	0.95
Imputation: wave 2	-2.01	0.13	0.02 - 0.76	0.02
PC4	12.05	$1.71x10^{5}$	5.8 - $5.03x10^{9}$	0.02
PC6	-7.67	0.00	$3.27x10^{-8}$ - 6.63	0.12
PC7	-6.70	0.00	$2.08x10^{-7}$ - 7.3	0.13
PC10	-9.63	$6.59x10^{-5}$	$3.27x10^{-8}$ - 0.13	0.01
SCZ-PRS at pT=1	**0.00**	**1.00**	**0.96 - 1.03**	**0.88**

Supplementary table 6.: Full results (standardized correlation coefficient, t-value and p-value) for the linear regression on age at onset in the USA sites (Baltimore, Iowa City, Rochester, Bethesda and San Diego) and BD-PRS. Variables, found to be associated with age at onset using backward regression were included as covariates. (p=1, t=-0.00, standardized beta=0.00, R^2 change=-0.026%)

	Standardized correlation coefficient	t-value	p-value
(Intercept)		3.74	0.00
Age at interview	0.37	7.24	0.00
Centre 8: Iowa City (USA)	0.00	-1.33	0.18
Centre 11: Rochester (USA)	0.00	-1.09	0.28
Centre 12: Bethesda (USA)	-3.33	-1.78	0.08
Centre 17: San Diego (USA)	-9.37	-3.36	0.00
Chip 5: Illumina HumanOmniExpress 1.0	-0.13	-0.44	0.66
Chip 7: Affymetrix 6.0	-0.50	-2.79	0.01
PC5	8.85	1.46	0.15
PC9	-11.12	-1.54	0.12
BD-PRS at pT=1	**0.00**	**0.00**	**1.00**

Supplementary table 7.: Full results (standardized correlation coefficient, t-value and p-value) for the linear regression on age at onset in the USA sites (Baltimore, Iowa City, Rochester, Bethesda and San Diego) and SCZ-PRS. Variables, found to be associated with age at onset using backward regression were included as covariates. (p=0.63, t=-0.48, standardized beta=0.00, R^2 change =-0.02%)

	Standardized correlation coefficient	t-value	p-value
(Intercept)		3.63	0.00
Age at interview	0.37	7.29	0.00
Centre 8: Iowa City (USA)	0.00	-1.34	0.18
Centre 11: Rochester (USA)	0.00	-1.09	0.28
Centre 12: Bethesda (USA)	-1.53	-1.77	0.08

Centre 17: San Diego (USA)	-9.41	-3.41	0.00
Chip 5: Illumina HumanOmniExpress 1.0	-0.12	-0.41	0.68
Chip 7: Affymetrix 6.0	-0.49	-2.78	0.01
PC5	8.86	1.46	0.15
PC9	-10.78	-1.49	0.14
SCZ-PRS at pT=1	**0.00**	**-0.48**	**0.63**

Supplementary table 8.: Full results (standardized correlation coefficient, t-value and p-value) for the linear regression on age at onset in the European, Canadian and Australian sites and BD-PRS. Variables, found to be associated with age at onset using backward regression were included as covariates. (p=0.48, t=-0.71, standardized beta=0.00, R^2 change=-0.03%)

	Standardized correlation coefficient	t-value	p-value
(Intercept)		4.26	0.00
Age at interview	0.37	22.65	0.00
Centre 2: Barcelona (Catalonia	1.96	1.18	0.24
Centre 3: Cagliari (Italy)	2.00	1.44	0.15
Centre 4: Halifax (Canada)	-3.81	-2.44	0.01
Centre 5: Dresden (Germany)	1.76	0.50	0.62
Centre 6: Graz (Austria)	0.48	0.12	0.90
Centre 9: Napoli (Italy)	2.46	1.32	0.19
Centre 10: PsyCourse study (Germany/Austria)	1.80	1.34	0.18
Centre 13: Paris (France)	0.65	0.35	0.72
Centre 14: Poznan (Poland)	1.19	0.71	0.48
Centre 15: Prague (Czech Republic)	4.05	2.18	0.03
Centre 16: Bucharest (Romania)	-2.84	-1.51	0.13
Centre 18: Stockholm (Sweden)	-2.15	-0.56	0.58
Centre 19: Sydney (Australia)	-1.77	-0.43	0.67
Centre 20: Würzburg (Germany)	2.02	1.17	0.24
Centre 21: Mannheim/Bonn (Germany)	2.60	1.93	0.05
Chip 2: Illumina Human610	-1.52	-0.38	0.70
Chip 3: Illumina Human 660W	-0.34	-0.20	0.84
Chip 5: Illumina HumanOmniExpress 1.0	-0.04	-0.01	0.99
Chip 7: Affymetrix 6.0	0.98	0.26	0.79
Chip 8: Illumina HumanOmni1-Quad	4.16	3.26	0.00
PC4	-17.13	-1.90	0.06
PC6	17.15	1.90	0.06
PC8	21.08	2.22	0.03
BD-PRS at pT=1	**-0.03**	**-0.71**	**0.48**

Supplementary table 9.: Full results (standardized correlation coefficient, t-value and p-value) for the linear regression on age at onset in the European, Canadian and Australian sites and SCZ-PRS. Variables, found to be associated

with age at onset using backward regression were included as covariates. (p=0.88, t=0.15, standardized beta=0.00, R^2 change =-0.02%)

	Standardized correlation coefficient	t-value	p-value
(Intercept)		4.55	0.00
Age at interview	0.50	22.62	0.00
Centre 2: Barcelona (Catalonia)	0.88	1.19	0.23
Centre 3: Cagliari (Italy)	0.50	1.48	0.14
Centre 4: Halifax (Canada)	-0.01	-2.43	0.02
Centre 5: Dresden (Germany)	0.00	0.49	0.63
Centre 6: Graz (Austria)	0.00	0.13	0.90
Centre 9: Napoli (Italy)	0.79	1.35	0.18
Centre 10: PsyCourse study (Germany/Austria)	2.57	1.43	0.15
Centre 13: Paris (France)	0.29	0.36	0.72
Centre 14: Poznan (Poland)	0.33	0.81	0.42
Centre 15: Prague (Czech Republic)	0.01	2.23	0.03
Centre 16: Bucharest (Romania)	-0.01	-1.46	0.14
Centre 18: Stockholm (Sweden)	0.00	-0.56	0.58
Centre 19: Sydney (Australia)	-0.54	-0.42	0.67
Centre 20: Würzburg (Germany)	2.76	1.19	0.23
Centre 21: Mannheim/Bonn (Germany)	1.20	2.01	0.04
Chip 2: Illumina Human610	-0.34	-0.35	0.72
Chip 3: Illumina Human 660W	0.00	-0.16	0.87
Chip 5: Illumina HumanOmniExpress 1.0	0.00	0.00	1.00
Chip 7: Affymetrix 6.0	0.00	0.29	0.77
Chip 8: Illumina HumanOmni1-Quad	1.32	3.30	0.00
PC4	-22.23	-1.84	0.07
PC6	7.50	1.88	0.06
PC8	5.14	2.23	0.03
SCZ-PRS at pT=1	**0.00**	**0.15**	**0.88**

3. Paper II

***Kalman, J.L.**, Olde Loohuis L., Vreeker A., [...], Andlauer T.F.M., Schulze T.G., Ophoff R., (2021). Characterization of Age and Polarity at Onset in Bipolar Disorder. The British Journal of Psychiatry, in press*

Given the large sample size and the complexity of the study and in accordance with the publication practice in the field of genetics, the study has three equally contributing first (**J.L.K.,** L.O.L., and A.V.) and last (T.F.M.A, T.G.S., and R.O.) authors. The contribution of each of the equally contributing coauthors is listed below. The contribution of Janos L. Kalman (J.L.K.) is highlighted.

The study was conducted under the supervision of T.F.M.A., and T.G.S. and R.O. (shared last authors). The research was designed by **J.L.K.,** L.O.L, A.V. and T.F.M.A in consultation with T.G.S. and R.O. **J.L.K.** reached out to the PIs of the individual cohorts, coordinated the transfer of the phenotype and genetic data, performed the quality control of the acquired data and coordinated the work throughout the study period. L.O.L. imputed the genetic data and calculated the heritability of the investigated phenotypes. **J.L.K.,** with the support of T.F.M.A. run the GWAS on age and polarity at onset and calculated the PGS. A.V. performed the statistical analysis on the phenotype data. **J.L.K.,** L.O.L, A.V., and T.F.M.A, wrote the manuscript. **J.L.K.** accompanied the publication process as corresponding author. All co-authors critically revised and approved the manuscript.

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Characterisation of age and polarity at onset in bipolar disorder

Janos L. Kalman*, Loes M. Olde Loohuis*, Annabel Vreeker*, Andrew McQuillin, Eli A. Stahl, Douglas Ruderfer, Maria Grigoroiu-Serbanescu, Georgia Panagiotaropoulou, Stephan Ripke, Tim B. Bigdeli, Frederike Stein, Tina Meller, Susanne Meinert, Helena Pelin, Fabian Streit, Sergi Papiol, Mark J. Adams, Rolf Adolfsson, Kristina Adorjan, Ingrid Agartz, Sofie R. Aminoff, Heike Anderson-Schmidt, Ole A. Andreassen, Raffaella Ardau, Jean-Michel Aubry, Ceylan Balaban, Nicholas Bass, Bernhard T. Baune, Frank Bellivier, Antoni Benabarre, Susanne Bengesser, Wade H Berrettini, Marco P. Boks, Evelyn J. Bromet, Katharina Brosch, Monika Budde, William Byerley, Pablo Cervantes, Catina Chillotti, Sven Cichon, Scott R. Clark, Ashley L. Comes, Aiden Corvin, William Coryell, Nick Craddock, David W. Craig, Paul E. Croarkin, Cristiana Cruceanu, Piotr M. Czerski, Nina Dalkner, Udo Dannlowski, Franziska Degenhardt, Maria Del Zompo, J. Raymond DePaulo, Srdjan Djurovic, Howard J. Edenberg, Mariam Al Eissa, Torbjørn Elvsåshagen, Bruno Etain, Ayman H. Fanous, Frederike Fellendorf, Alessia Fiorentino, Andreas J. Forstner, Mark A. Frye, Janice M. Fullerton, Katrin Gade, Julie Garnham, Elliot Gershon, Michael Gill, Fernando S. Goes, Katherine Gordon-Smith, Paul Grof, Jose Guzman-Parra, Tim Hahn, Roland Hasler, Maria Heilbronner, Urs Heilbronner, Stephane Jamain, Esther Jimenez, Ian Jones, Lisa Jones, Lina Jonsson, Rene S. Kahn, John R. Kelsoe, James L. Kennedy, Tilo Kircher, George Kirov, Sarah Kittel-Schneider, Farah Klöhn-Saghatolislam, James A. Knowles, Thorsten M. Kranz, Trine Vik Lagerberg, Mikael Landen, William B. Lawson, Marion Leboyer, Qingqin S. Li, Mario Maj, Dolores Malaspina, Mirko Manchia, Fermin Mayoral, Susan L. McElroy, Melvin G. McInnis, Andrew M. McIntosh, Helena Medeiros, Ingrid Melle, Vihra Milanova, Philip B. Mitchell, Palmiero Monteleone, Alessio Maria Monteleone, Markus M. Nöthen, Tomas Novak, John I. Nurnberger, Niamh O'Brien, Kevin S. O'Connell, Claire O'Donovan, Michael C. O'Donovan, Nils Opel, Abigail Ortiz, Michael J. Owen, Erik Pålsson, Carlos Pato, Michele T. Pato, Joanna Pawlak, Julia-Katharina Pfarr, Claudia Pisanu, James B. Potash, Mark H Rapaport, Daniela Reich-Erkelenz, Andreas Reif, Eva Reininghaus, Jonathan Repple, Hélène Richard-Lepouriel, Marcella Rietschel, Kai Ringwald, Gloria Roberts, Guy Rouleau, Sabrina Schaupp, William A Scheftner, Simon Schmitt, Peter R. Schofield, K. Oliver Schubert, Eva C. Schulte, Barbara Schweizer, Fanny Senner, Giovanni Severino, Sally Sharp, Claire Slaney, Olav B. Smeland, Janet L. Sobell, Alessio Squassina, Pavla Stopkova, John Strauss, Alfonso Tortorella, Gustavo Turecki, Joanna Twarowska-Hauser, Marin Veldic, Eduard Vieta, John B. Vincent, Wei Xu, Clement C. Zai, Peter P. Zandi, Psychiatric Genomics Consortium (PGC) Bipolar Disorder Working Group, International Consortium on Lithium Genetics (ConLiGen) Colombia-US Cross Disorder Collaboration in Psychiatric Genetics, Arianna Di Florio, Jordan W. Smoller, Joanna M. Biernacka, Francis J. McMahon, Martin Alda, Bertram Müller-Myhsok, Nikolaos Koutsouleris, Peter Falkai, Nelson B. Freimer, Till F.M. Andlauer†, Thomas G. Schulze† and Roel A. Ophoff†

Background

Studying phenotypic and genetic characteristics of age at onset (AAO) and polarity at onset (PAO) in bipolar disorder can provide new insights into disease pathology and facilitate the development of screening tools.

Aims

To examine the genetic architecture of AAO and PAO and their association with bipolar disorder disease characteristics.

Method

Genome-wide association studies (GWASs) and polygenic score (PGS) analyses of AAO ($n = 12\,977$) and PAO ($n = 6773$) were conducted in patients with bipolar disorder from 34 cohorts and a replication sample ($n = 2237$). The association of onset with disease characteristics was investigated in two of these cohorts.

Results

Earlier AAO was associated with a higher probability of psychotic symptoms, suicidality, lower educational attainment, not living together and fewer episodes. Depressive onset correlated with suicidality and manic onset correlated with delusions and manic episodes. Systematic differences in AAO between cohorts and continents of origin were observed. This was also reflected in single-nucleotide variant-based heritability estimates, with higher heritabilities for stricter onset definitions. Increased PGS for autism spectrum disorder (β = –0.34 years, s.e. = 0.08), major depression (β = –0.34 years, s.e. = 0.08), schizophrenia (β = –0.39 years, s.e. = 0.08), and educational attainment (β = –0.31 years, s.e. = 0.08) were associated with an earlier AAO. The AAO GWAS identified one significant locus, but this finding did not replicate. Neither GWAS nor PGS analyses yielded significant associations with PAO.

Conclusions

AAO and PAO are associated with indicators of bipolar disorder severity. Individuals with an earlier onset show an increased polygenic liability for a broad spectrum of psychiatric traits. Systematic differences in AAO across cohorts, continents and phenotype definitions introduce significant heterogeneity, affecting analyses.

Keywords

Bipolar disorder; age at onset; polarity at onset; GWAS; polygenic score.

Background

Bipolar disorder is highly heritable and affects approximately 1% of the population. It has a recurrent or chronic course and is associated with psychosocial impairment and reduced functioning, and it is a

* Joint first authors.
† Joint last authors.

leading cause of global disease burden.[1] Individuals usually experience their first (hypo)manic or depressive episode of bipolar disorder in adolescence or early adulthood, but often they are not diagnosed until 5 to 10 years later,[2] especially in individuals with an earlier age at onset (AAO) or a depressive index episode.[3] Early illness onset is associated with a more severe disease course and greater impairment across a wide range of mental and physical disorders and is a useful prognostic marker.[4–7] However, pathophysiological processes leading to a disorder are thought to begin long before the first symptoms appear.[8,9] Investigating the factors contributing to age and polarity (i.e. either a (hypo)manic or depressive episode) at onset could thus improve our understanding of disease pathophysiology and facilitate development of personalised screening and preventive measures. Accordingly, AAO and polarity at onset (PAO) of bipolar disorder are considered as suitable phenotypes for genetic analyses.

Genome-wide association studies (GWASs) have improved our understanding of the genetic architecture of susceptibility to bipolar disorder; however, the genetic determinants of AAO and PAO remain largely unknown. Evidence suggests that patients with an early AAO carry a stronger genetic loading for bipolar disorder risk.[10] For example, an earlier parental AAO increases familial risk for bipolar disorder and is one of the strongest predictors of 5-year illness onset in affected offspring.[10–12] Previous research has described that a higher genetic risk burden for schizophrenia may be associated with earlier AAO of bipolar disorder,[13] but this finding did not replicate.[14–16] Moreover, a recent study did not find an association of bipolar disorder polygenic score (PGS) with AAO.[17] Thus far, GWASs for age at bipolar disorder onset have been underpowered,[18,19] and a study of 8610 patients found no significant evidence for a heritable component contributing to onset age.[13] The PAO was shown to cluster in families,[20] but the genetic architecture of PAO has not yet been investigated.

Aims

To fill these knowledge gaps, we performed comprehensive analyses of AAO and PAO of bipolar disorder in the largest sample studied to date by (a) examining phenotype definitions and associations, (b) investigating whether the genetic load for neuropsychiatric disorders and traits contributes to AAO and PAO of bipolar disorder, and (c) conducting systematic GWASs.

Method

References to published methods are listed in Supplementary Note 1 available at https://doi.org/10.1192/bjp.2021.102.

Study samples

Participants with a bipolar disorder diagnosis, available genetic data and AAO information were selected from independent data-sets, including those previously submitted to the Psychiatric Genomics Consortium (PGC) Bipolar Disorder Working Group[13] and the International Consortium on Lithium Genetics (ConLiGen).[21] These consortia aggregate genetic data from many cohorts worldwide. Our analyses comprised 34 cohorts with 12 977 patients with bipolar disorder who have European ancestry from Europe, North America and Australia. For a description of sample ascertainment, see the Supplementary Material.

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human patients were approved by the local ethics committees, and written informed consent was obtained from all patients. For details on the data-sets, including phenotype definitions and distributions, see Table 1, Fig. 1, and Supplementary Table S1.

Definition of AAO

The definition of age at bipolar disorder onset differed by cohort. To enhance cross-cohort comparability, we grouped the definitions into four broad categories as follows (Supplementary Table S1).

(a) Diagnostic interview: age at which the patient first experienced a (hypo)manic, mixed or major depressive episode according to a standardised diagnostic interview.
(b) Impairment/help-seeking: age at which symptoms began to cause subjective distress or impaired functioning or at which the patient first sought psychiatric treatment.
(c) Pharmacotherapy: age at first administration of medication.
(d) Mixed: a combination of the above-mentioned definitions.

Across definitions, participants younger than 8 years at onset were excluded (n = 279) because of the uncertainty about the reliability of retrospective recall of early childhood onset. The distribution of AAO was highly skewed and differed considerably between the cohorts (Table 1 and Fig. 1). Therefore, we transformed AAO in each cohort by rank-based inverse-normal transformation and used this normalised variable as the primary dependent variable in all genetic analyses. To facilitate interpretability of effect sizes, we also report results of the corresponding untransformed AAO.

Definition of PAO

For each cohort, PAO was defined by comparing the age at the first (hypo)manic and first depressive episode or using the polarity variable provided by the cohort. Specifically, patients were divided into three subgroups:

(a) (hypo)mania before depression (PAO-M);
(b) depression before (hypo)mania (PAO-D); and
(c) mixed (PAO-X).

The third category included patients with mixed episodes and those with a first (hypo)manic and depressive episode within the same year (Table 1). In the primary analysis, we combined patients with (hypo)mania and mixed onset and assigned this as the reference category. In secondary analyses, we excluded the patients in the mixed group.

Phenotypic disease characteristics

We performed phenotypic analyses of disease onset in patients with bipolar disorder type I from three cohorts: the Dutch Bipolar cohort ($n = 1313$)[22] and the German PsyCourse[23] and FOR2107[24] cohorts, which were analysed jointly ($n = 346$). We analysed the following disease characteristics, which were previously reported as being associated with disease onset and were assessed in a similar way across cohorts: lifetime delusions, lifetime hallucinations, history of suicide attempt, suicidal ideation, current smoking, educational attainment, living together with a partner, and frequency of manic and depressive episodes per year. For more detailed information, see the Supplementary Note 2 and Supplementary Table S9.

Quality control and imputation of genotype data

The cohorts were genotyped according to local protocols. Individual genotype data of all discovery-stage cohorts were processed with the PGC Rapid Imputation and Computational Pipeline for GWAS (RICOPILI) with the default parameters for standardised quality control, imputation and analysis. Before imputation, filters for the removal of variants included non-autosomal chromosomes, missingness ≥0.02, and a Hardy–Weinberg equilibrium test $P < 1 \times 10^{-10}$.

Table 1 Sample characteristics of data-sets used in genetic analyses

GWAS stage, dataset	*n*	Continent	Diagnosis, % bipolar disorder type I	Gender, % male	AAO, median (MAD,[a] range)	Definition of AAO	PAO,[b] *n* (%)
Discovery							
wtccc	1452	Europe	89.53	36.85	24 (8.9, 9–63)	Impairment/help-seeking	
tgco2	865	North America	100	33.64	17 (5.93, 8–46)	Diagnostic interview	PAO-M: 316 (38.92); PAO-D: 496 (61.08)
gain	797	North America	100	48.06	18 (5.93, 8–45)	Diagnostic interview	PAO-M: 135 (18.57); PAO-D: 440 (60.52)
stp1	718	North America	100	44.01	16 (5.93, 8–41)	Diagnostic interview	PAO-M: 137 (19.08); PAO-D: 420 (58.5)
gsk1	715	North America	89.51	36.36	19 (7.51, 8–52)	Diagnostic interview	PAO-M: 102 (14.61); PAO-D: 395 (56.59)
usc2	681	North America	96.18	47.58	18 (7.41, 8–48)	Impairment/help-seeking	
bonn	638	Europe	99.84	47.34	25 (8.9, 9–64)	Impairment/help-seeking	
ucl2	604	Europe	100	44.37	30 (11.86, 9–60)	Pharmacotherapy	PAO-M: 47 (9.96); PAO-D: 209 (44.28)
bmg3	455	Europe	57.14	40.66	24 (10.38, 10–62)	Impairment/help-seeking	PAO-M: 43 (16.35); PAO-D: 159 (60.46)
m&m's	449	Europe	74.83	52.12	23 (10.38, 8–65)	Mixed	PAO-M: 73 (17.14); PAO-D: 238 (55.87)
uclo	439	Europe	100	39.86	22 (7.41, 8–51)	Impairment/help-seeking	PAO-M: 54 (14.25); PAO-D: 197 (51.98)
fran	411	Europe	77.62	41.36	22 (7.41, 10–58)	Diagnostic interview	
euoR	410	Europe	75.85	44.15	22 (9.64, 11–59)	Mixed	
hal2	355	North America	71.55	42.54	23 (8.9, 8–56)	Diagnostic interview	PAO-M: 102 (29.65); PAO-D: 213 (61.92)
ume4	354	Europe	69.21	37.85	20 (8.9, 8–63)	Diagnostic interview	PAO-M: 54 (14.25); PAO-D: 197 (51.98)
swa2	344	Europe	81.10	41.86	23 (10.38, 10–70)	Impairment/help-seeking	
bmpo	319	Europe	78.06	39.18	28 (11.86, 10–63)	Impairment/help-seeking	PAO-M: 41 (16.33); PAO-D: 150 (59.76)
top7	301	Europe	62.79	41.53	19 (7.41, 8–49)	Diagnostic interview	
may1	257	North America	100	45.14	20 (8.9, 8–62)	Diagnostic interview	PAO-M: 34 (13.23); PAO-D: 142 (55.25)
bmsp	248	Europe	94.76	45.56	22 (7.41, 9–57)	Impairment/help-seeking	PAO-M: 24 (10.04); PAO-D: 93 (38.91)
bmau	245	Australia	79.18	40.82	19 (7.41, 8–55)	Diagnostic interview	PAO-M: 46 (20.18); PAO-D: 125 (54.82)
edi1	244	Europe	99.18	42.62	20 (5.93, 13–50)	Diagnostic interview	
rom3	226	Europe	100	41.15	25 (10.38, 12–59)	Diagnostic interview	PAO-M: 91 (40.27); PAO-D: 134 (59.29)
butr	204	Europe	100	40.2	22 (5.19, 13–44)	Impairment/help-seeking	
euol	191	Europe	74.87	31.41	24 (8.9, 13–67)	Diagnostic interview	PAO-M: 48 (27.43); PAO-D: 98 (56)
ageu	178	Europe	90.45	39.33	21 (7.41, 8–51)	Impairment/help-seeking	
mich	169	North America	100	31.36	18 (5.93, 8–45)	Diagnostic interview	PAO-M: 42 (24.85); PAO-D: 84 (49.7)
naom	159	North America	84.91	44.65	18 (7.41, 8–66)	Mixed	PAO-M: 30 (28.85); PAO-D: 51 (49.04)
bmg2	152	Europe	59.87	35.53	27 (10.38, 13–63)	Impairment/help-seeking	
top8	111	Europe	55.86	37.84	18 (7.41, 8–49)	Diagnostic interview	
h66x	92	Europe	82.61	36.96	30 (10.38, 9–55)	Mixed	
auom	85	Australia	88.24	45.88	25 (10.38, 8–64)	Diagnostic interview	
euo2	58	Europe	65.52	56.9	26 (8.9, 18–57)	Diagnostic interview	
dub1	51	Europe	100	54.9	21 (5.93, 12–45)	Diagnostic interview	
Summary	12 977		88.27	41.57	21 (8.9, 8–70)		PAO–M: 1435 (21.19); PAO-D: 3885 (57.36)
Replication							
ukwa1	1156	Europe	75.17	38.15	23 (8.9, 8–74)	Impairment/help-seeking	
dutch	468	Europe	100	42.31	28 (10.38, 11–63)	Pharmacotherapy	
jst5	186	North America	100	53.23	16 (7.41, 8–51)	Unknown	
colo	176	South America	90.34	31.82	20 (11.86, 8–52)	Diagnostic interview	
bmrom	126	Europe	100	42.86	24 (8.9, 12–56)	Diagnostic criteria	
bdtrs	125	Europe	64	45.6	28 (13.34, 8–65)	Impairment/help-seeking	
Summary	2237		84.40	40.46	24 (10.38, 8–74)		
All data	15 214		86.26	41.41	22 (8.9, 8–74)		

GWAS, genome-wide association study; AAO, age at onset; MAD, median absolute deviation, PAO, polarity at onset; PAO-M, mania/hypomania before depression; PAO-D, depression before mania/hypomania.
a. We calculated the median absolute deviation using 1.4826 as constant.
b. We defined three categories of polarity at onset: PAO-M, mania/hypomania before depression; PAO-D, depression before mania/hypomania; and PAO-X, mixed. PAO was not available for all patients. The table presents the PAO-M and PAO-D subgroups and their percentage within the individual cohorts.

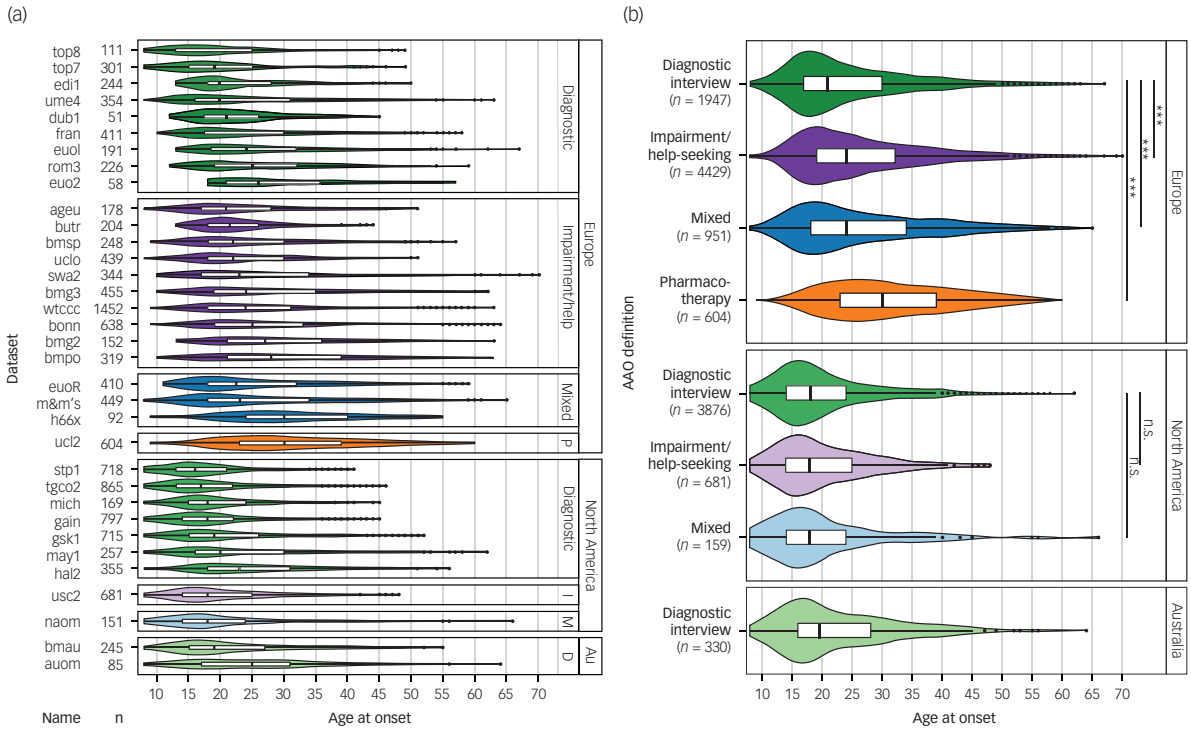

Fig. 1 Differences between phenotype definitions and continents across the 34 data-sets used for discovery-stage genetic analyses.

(a) The various data-sets used four different definitions for age at onset: diagnostic interview, impairment/help-seeking, pharmacotherapy and mixed. (b) The untransformed age at onset differed significantly between cohorts, depending on the phenotype definition used and the continent of origin.
Au, Australia; Diagnostic, diagnostic interview; D, diagnostic interview; I, impairment/help-seeking; M, mixed; P, pharmacotherapy. n.s., not significant; $P > 0.05$; *** $P < 0.001$.

Individuals were removed if they showed a genotyping rate ≤0.98, absolute deviation in autosomal heterozygosity of F_{het} ≥0.2, or a deviation >4 s.d.s from the mean in any of the first eight ancestry components within each cohort. From genetic duplicates and relatives (pi-hat >0.2) across all samples, only the individual with more complete phenotypic information on AAO and PAO, gender and diagnosis was retained. Imputation was performed by IMPUTE2 with the Haplotype Reference Consortium reference panel.

PGS

We calculated PGS based on prior GWAS of attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), bipolar disorder, educational attainment (measured as 'years in education'), major depression (MD), and schizophrenia (see Supplementary Table S3, which includes references). PGS weights were estimated with PRS-CS(see Supplement), with six scores per GWAS (with φ = 1×10^{-1}, 1×10^{-2}, 1×10^{-3}, 1×10^{-4}, 1×10^{-5}, and 1×10^{-6}). We tested the associations of the PGS with the AAO and PAO by linear and logistic regressions, respectively. Gender, bipolar disorder subtype and the first eight ancestry components were included as covariates. The significance threshold was Bonferroni-corrected for 96 tests (α = 0.05/(6 φ thresholds × 8 traits × 2 phenotypes) = 5.2×10^{-4}).

GWASs

We performed a discovery GWAS on the 34 cohorts (n = 12 977) and replication analyses in six additional cohorts with $n = 2237$ patients with bipolar disorder. As a first step, we conducted individual GWAS for each cohort with 40 or more patients using the RICOPILI workflow, using the same covariates as in the PGS analyses. Sample sizes are provided in Supplementary Tables S2 and S7. The resulting GWAS did not show an inflation of test statistics for any of the cohorts, indicating limited population stratification (Supplementary Table S2). Next, we performed a fixed-effects meta-analysis using METAL, combining the cohort-specific GWASs. For the meta-analysis summary statistics, we applied the following variant-level post-quality control parameters: imputation INFO score ≥0.9, minor allele frequency (MAF) ≥0.05, and successfully imputed/genotyped in more than half of the cohorts.

The primary analyses were AAO (normalised, analysed by linear regression) and PAO (analysed by logistic regression). Secondary analyses included GWASs stratified by AAO definition and continent of origin.

We estimated the power to replicate our initial genome-wide significant finding from the discovery GWAS based on the regression coefficients using the *pwr* package in *R*. Assuming the same effect size and MAF (beta 0.075, allele frequency 0.32) and a standardised phenotype, we had 76% power to detect the effect in our sample size of 2237 at an alpha level of 0.1. For comparison, we had 57% power to detect the effect in our discovery sample, using the more stringent genome-wide significance cut-off.

Heritability analyses

Next, we assessed the overall variance in AAO and PAO explained by genotyped variants (so-called single-nucleotide variant (SNV)-based heritability, h^2_{SNV}). For the only individual cohort with more than 1000 samples, we estimated h^2_{SNV} with GCTA GREML. In this case, we validated the robustness of the h^2_{SNV} estimate with

Table 2 The association of age and polarity at onset with disease characteristics in two European bipolar disorder cohorts

	AAO					PAO				
Disease characteristic	*n*	Odds ratio	95% CI	Unadjusted *P*	Adjusted *P*[a]	*n*	Odds ratio	95% CI	Unadjusted *P*	Adjusted *P*
Delusions	1612	0.71	0.64–0.79	1.61×10^{-9}	$1.45 \times 10^{-8*}$	1298	0.62	0.49–0.79	1.04×10^{-4}	$6.24 \times 10^{-4*}$
Hallucinations	1594	0.83	0.74–0.92	3.5×10^{-4}	$1.40 \times 10^{-3*}$	1290	0.93	0.74–1.17	5.22×10^{-1}	1.00×10^{0}
Current smoking	1594	0.98	0.89–1.09	7.50×10^{-1}	7.50×10^{-1}	1282	1.12	0.89–1.41	3.39×10^{-1}	1.00×10^{0}
Suicidal ideation	1518	0.79	0.71–0.88	2.31×10^{-5}	$1.62 \times 10^{-4*}$	1280	1.68	1.32–2.13	2.11×10^{-5}	$1.48 \times 10^{-4*}$
Suicide attempt	1537	0.78	0.69–0.88	2.73×10^{-5}	$1.64 \times 10^{-4*}$	1262	1.58	1.24–2.02	2.67×10^{-4}	$1.34 \times 10^{-3*}$
Educational attainment	1636	1.17	1.06–1.29	2.77×10^{-3}	$8.31 \times 10^{-3*}$	1319	1.06	0.85–1.33	5.93×10^{-1}	1.00×10^{0}
Living together	1357	1.28	1.15–1.44	1.01×10^{-5}	$8.08 \times 10^{-5*}$	–	–	–	–	–

AAO, age at onset; PAO, polarity at onset; *n*, total number of participants from the Dutch and German cohorts.
* $P < 0.05$
a. After Bonferroni–Holm correction.

the mean of 1000 × resampling of 95% of the sample. To estimate the overall heritability of the meta-analysis summary statistics we estimated h^2_{SNV} by linkage disequilibrium score regression, for each GWAS with sample size >3000. The 95% CIs were constrained to a minimum of 0 and a maximum of 1.

Results

Heterogeneity of AAO and PAO across cohorts

Among the four definitions of AAO across the 34 cohorts, impairment/help-seeking was the most common in Europe and diagnostic interview the most common in North America (Table 1, Fig. 1). Across all cohorts, the median AAO was 21 years (range of medians: 16–30 years; Fig. 1). However, substantial differences in the AAO were observed between subgroups: first, the median untransformed AAO was lower in bipolar disorder type I than in type II (type I, 21 years; type II, 22 years; Kruskal-Wallis test $P = 1.8 \times 10^{-4}$; Supplementary Table S6).

Second, the AAO was lower when determined by diagnostic interview compared with other phenotype definitions (diagnostic interview, 19 years; impairment/help-seeking, 23 years; pharmacotherapy, 30 years; mixed, 22 years; $P = 2.96 \times 10^{-191}$). Third, the age was lower in North America compared with Europe (Europe, 24 years; North America, 18 years; and Australia, 19.5 years; $P = 2.0 \times 10^{-263}$). These differences across continents remained significant when including onset definitions and bipolar disorder subtype in a multivariable regression model, indicating that they are likely partially independent from the assessment strategy (Supplementary Table S6).

The majority of patients reported a depression-first PAO. Patients with depression-first were less frequent in the impairment/help-seeking than in the diagnostic interview category (55% and 60%, respectively; $P = 4.5 \times 10^{-4}$, Supplementary Fig. S1), but their proportions were similar between Europe and North America (57% and 59%, respectively; $P = 0.17$ test of proportion).

Analyses of disease characteristics

In a meta-analysis of the Dutch and German samples, earlier AAO was significantly associated with a higher probability of lifetime delusions, hallucinations, suicide attempts, suicidal ideation, lower educational attainment and not living together (Table 2, Supplementary Tables S4 and S5). A later AAO was positively significantly correlated with a higher number of manic and depressive episodes per year (see Tables 3, and the Supplementary Note 2). Moreover, a (hypo)manic onset was significantly associated with a greater likelihood of delusions and more manic episodes per year, whereas a depressive onset was associated with a higher probability of suicidal ideation and lifetime suicide attempts.

Associations of PGSs with AAO and PAO

Next, we conducted analyses to evaluate whether the genetic liability for five psychiatric disorders and educational attainment were associated with the age at disease onset (Fig. 2(a) and (b) and Supplementary Table S8). After correcting for 96 tests, higher PGSs for ASD ($\beta = -0.34$ years per 1 s.d. increase in PGS, s.e. = 0.08, $P = 9.85 \times 10^{-6}$), major depression ($\beta = -0.34$, s.e. = 0.08, $P = 1.40 \times 10^{-6}$), schizophrenia ($\beta = -0.39$, s.e. = 0.08, $P = 2.91 \times 10^{-6}$) and educational attainment ($\beta = -0.31$, s.e. = 0.08, $P = 5.58 \times 10^{-5}$) were significantly associated with an earlier age at bipolar disorder onset. This was not the case for ADHD or bipolar disorder PGS. No PGS was significantly associated with PAO (Supplementary Fig. S4, Supplementary Table S8).

GWASs

Next, we attempted to identify individual genetic loci associated with the AAO or PAO. In our discovery GWAS using 34 cohorts, one locus was significantly associated with AAO (rs1610275 on chromosome 16; minor allele G frequency = 0.319, $\beta = 0.075$ (s.e. = 0.014), $P = 3.39 \times 10^{-8}$, Fig. 2(c), Supplementary Table S7, Supplementary Fig. S2). This SNV mapped to an intron of the brain-expressed gene *FTO* (alpha-ketoglutarate dependent dioxygenase, Fig. 2(d)).

Table 3 The association of age and polarity at onset with manic and depressive episodes in two European bipolar disorder cohorts[a]

	AAO					PAO				
Episode	*n*	Estimate[b]	s.e.	Unadjusted *P*	Adjusted *P*[c]	*n*	Estimate	s.e.	Unadjusted *P*	Adjusted *P*
Number of manic episodes per illness year	1436	0.11	0.03	7.08×10^{-5}	$3.54 \times 10^{-4*}$	1156	−0.42	0.06	4.68×10^{-13}	$3.74 \times 10^{-12*}$
Number of depressive episodes per illness year	1231	0.07	0.03	1.93×10^{-2}	$3.86 \times 10^{-2*}$	1051	0.12	0.06	4.63×10^{-2}	1.85×10^{-1}

AAO, age at onset; PAO, polarity at onset; *n*, total number of participants from the Dutch and German cohorts.
* $P < 0.05$
a. The number of manic/depressive episodes was divided by (years of illness) + 1. For secondary analyses of the number of episodes not corrected for the years of illness, see the Supplementary Note 2.
b. Unstandardised beta coefficient.
c. After Bonferroni–Holm correction.

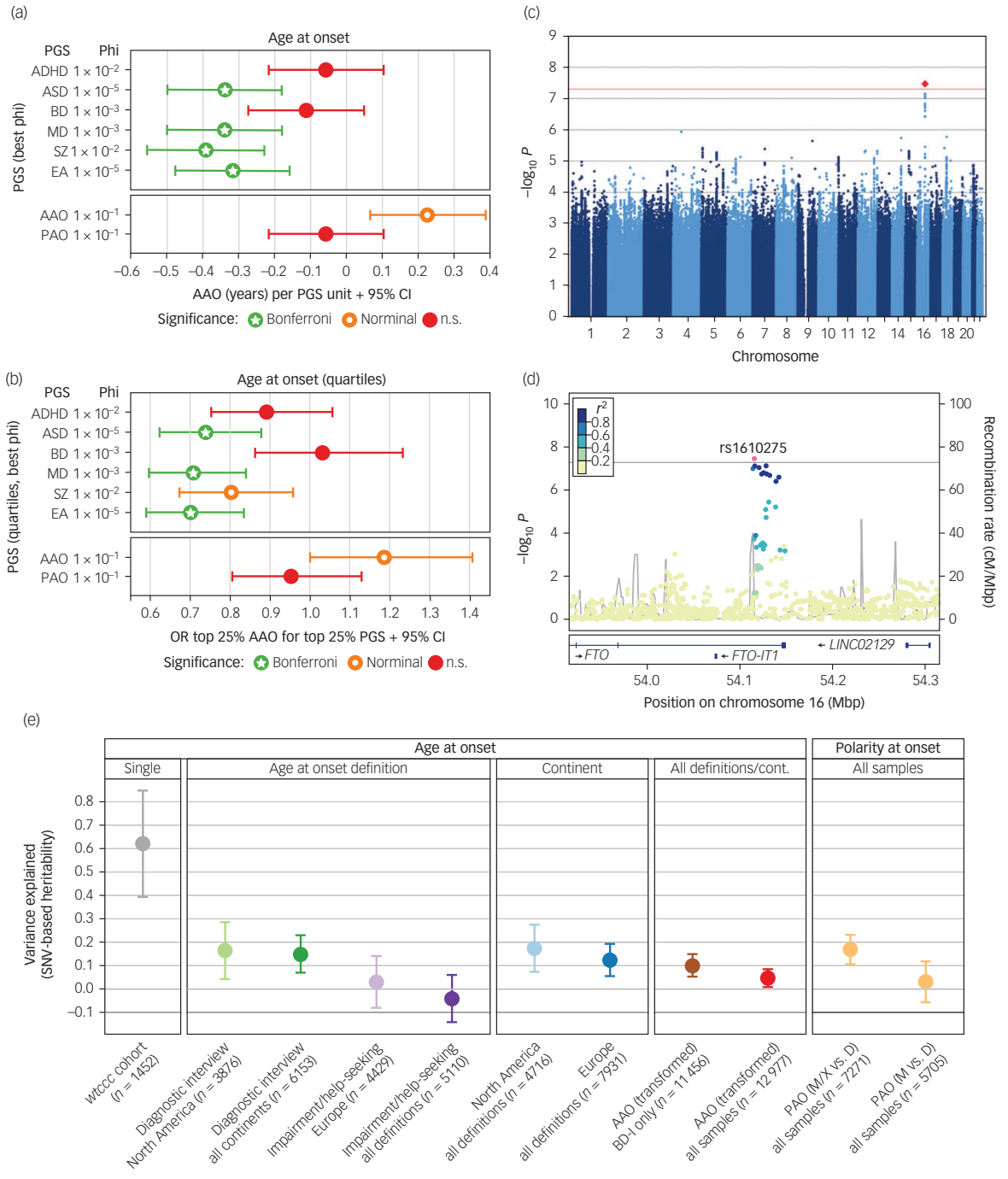

Fig. 2 Results from the genome-wide association study (GWAS), polygenic score (PGS) analyses, and heritability analyses.

(a) and (b) Results from analyses of PGS. For detailed results, see Supplementary Table S8. Significance levels: n.s., not significant, $P > 0.05$; nominal: $P < 0.05$; Bonferroni, below the Bonferroni-corrected significance threshold corrected for 96 tests ($P < 5.2 \times 10^{-4}$). (a) Associations of PGSs with the AAO. For interpretability, the plot shows the untransformed AAO. Significance levels are based on the analyses of the AAO after rank-based inverse-normal transformation (which was performed because the distribution of AAO was highly skewed and differed greatly across the study cohorts). (b) Associations of the top versus bottom AAO quartiles with the top versus bottom PGS quartiles. A higher odds ratio (OR) indicates an association with higher AAO. (c) Manhattan plot of the discovery-stage AAO GWAS. (d) Locus-specific Manhattan plot of the top-associated AAO variant. (e) Estimation of the variance in different phenotype definitions explained by genotyped single-nucleotide variants (SNV) (h^2_{SNV}). For the cohort *wtccc*, we directly estimated h^2_{SNV} from genotype data in GCTA GREML; we estimated all other heritabilities from GWAS summary statistics using LDSC. The plot shows h^2_{SNV} estimates and s.e.
ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; BD, bipolar disorder; cM, centi Morgan. Mbp, mega base pairs; MD, major depression; EA, educational attainment; SNV, single-nucleotide variant; cont, continent; disorder type I; PAO, polarity at onset; PAO-M, mania/hypomania before depression; PAO-D, depression before mania/hypomania; PAO-X, mixed; SZ, schizophrenia.

However, this association was not replicated in an independent sample of six cohorts (Supplementary Table S7, Supplementary Fig. S2). In the replication sample ($n = 2237$), we had 76% power to replicate this SNV at a P-value threshold of 0.1. The GWAS of PAO did not yield any genome-wide significant findings, in either primary (PAO-M/-X versus PAO-D) or secondary (PAO-M versus PAO-D) analyses (Supplementary Fig. S3).

We also calculated PGSs for AAO and PAO using leave-one-out summary statistics from these GWASs. The AAO PGS was nominally significantly associated with AAO ($\beta = 0.23$ years, s.e. = 0.08, $P = 0.0087$, $\varphi = 0.1$, Fig. 2(a) and 2(b)) for five of six tested φ parameters but did not withstand correction for multiple testing (Supplementary Table S8). The PAO PGS was not associated with the PAO (Supplementary Fig. S4).

SNV-based heritability of the investigated phenotypes

We estimated the SNV-based heritability h^2_{SNV} directly from genotype data using GCTA in the only cohort large enough for this analysis, *wtccc*. For the AAO, the h^2_{SNV} in *wtccc* was estimated at 0.63 ($P = 0.0026$) (Fig. 2(e)). We evaluated the robustness of this estimate by resampling (mean $h^2_{SNV} = 0.62$, resampling 95% CI 0.15–1.00).

We next estimated h^2_{SNV} by linkage disequilibrium score regression (LDSC) from the GWAS summary statistics generated in the present study (Fig. 2(e)). We observed that the heritability decreased when cohorts, phenotype definitions and continents were combined (for example 'diagnostic interview' in North America: AAO $h^2_{SNV} = 0.16$, 95% CI 0–0.40, 'impairment/help-seeking' in Europe: $h^2_{SNV} = 0.03$, 95% CI 0–0.25, all combined $h^2_{SNV} = 0.05$, 95% CI 0–0.12). As a result of the insufficient sample size, we could not estimate the h^2_{SNV} of impairment/help-seeking in North America and diagnostic interview in Europe. For depression versus (hypo) manic and mixed PAO, h^2_{SNV} was 0.17 (95% CI 0.05–0.29) on the observed scale.

Discussion

In our study of bipolar disorder disease onset, we first evaluated the association between AAO or PAO with several clinical indicators of severity in a sample of 1659 patients. We showed that an earlier onset is associated with increased severity, demonstrating and replicating the clinical relevance of these phenotypes. Next, we performed genetic analyses including 12 977 patients from 34 cohorts. Here, we demonstrated that higher genetic risk for ASD, major depression, schizophrenia and educational attainment is associated with an earlier AAO, providing evidence that the age at bipolar disorder onset is influenced by a broad liability for psychiatric illness.

Third, we performed GWAS to identify genetic variants associated with the AAO and PAO, which did not yield any replicated associations. Fourth, we outlined the extent to which age (and, partly, polarity) at onset varies across cohorts, depending both on the continent of recruitment and on the diagnostic instrument used to determine the AAO.

Finally, we showed that this substantial phenotypic heterogeneity affects the heritability of the phenotype, which decreased when multiple cohorts with different diagnostic instruments were combined. This analysis emphasises how genetic analyses are hampered by phenotypic heterogeneity.

Illness onset is associated with disease course

In a first set of analyses, we confirmed the clinical relevance of disease onset phenotypes in bipolar disorder. Age at bipolar disorder onset was associated with important illness severity indicators, such as suicidality, psychotic symptoms and lower educational attainment, thereby replicating findings of previous studies.[22,25] Furthermore, patients with a depressive bipolar disorder onset had an increased reported lifetime suicidality, whereas those with a (hypo)manic onset were more likely to experience delusions and more manic episodes per illness year. Contrary to previous evidence in a US (but not in a French) sample, we observed that an earlier onset was associated with fewer episodes per illness year.[26] Of note, when not normalising for the illness duration, the AAO was, as expected, positively correlated with the number of episodes (see Supplementary Note 2).

Increased genetic scores for neuropsychiatric phenotypes predict an earlier illness onset

Higher PGSs for schizophrenia, major depression, ASD and educational attainment were significantly associated with a lower AAO, and none of the tested PGSs were significantly associated with PAO. Our findings support the hypothesis that a general liability for psychiatric disorders influences an earlier age of onset in bipolar disorder. Alternatively, an earlier onset may also reflect the broader phenotypic spectrum sometimes captured in early-onset bipolar disorder. Unexpectedly, and in contrast to several other disorders (for example multiple sclerosis), where the strongest genetic risk factors for disease liability are also the most important genetic factors associated with an earlier disease onset,[6,27] we did not find a significant association between bipolar disorder PGS and the age at bipolar disorder onset. Statistical power may have influenced this result, as the sample sizes of both the schizophrenia and major depression GWASs were larger than that of the bipolar disorder GWAS, improving the predictive ability of these PGSs compared with the bipolar disorder PGS.

The described significant relationship of higher educational attainment PGS with an earlier AAO may seem counterintuitive. However, several studies described a significant association, genetic correlation and causal relationship between a higher educational attainment and bipolar disorder risk.[28,29] Our findings demonstrate that a high educational attainment PGS is not only a risk factor for bipolar disorder but also associated with an earlier onset of the disorder.

Lack of replication of the GWAS finding

We have conducted two GWASs to identify individual loci influencing the age and polarity at bipolar disorder onset, possibly independently of affecting lifetime disorder risk. Our discovery GWAS prioritised a genome-wide significant locus associated with the AAO. However, the lack of replication suggests that this finding may have been false-positive. This failure to replicate could have been because of insufficient statistical power in the replication sample, as our power analysis did not account for the likely phenotypic and genetic heterogeneity across cohorts and may thus have underestimated the necessary sample size. Importantly, the replication sample was more ethnically diverse than the discovery sample, which reduced the statistical power. The PAO GWAS, with its lower sample size and dichotomous phenotype, did not identify any genome-wide significant locus.

We also calculated an AAO PGS using our GWAS and tested it on our sample. Although the effect size of this PGS on the AAO was substantial (0.23 years per unit change in the PGS), the association was only nominally significant.

The heterogeneity of phenotype definitions

A striking finding of our study was the systematic difference in the AAO distribution across cohorts, continents and assessment strategies. Although the assessment strategies varied considerably by continent, with diagnostic interview being mainly used in North

America and impairment/help-seeking in Europe, we showed that the continent-level differences were partially independent from the AAO assessment strategy and that both factors contributed significantly to the heterogeneity (Supplementary Table S6). However, variations in the demographic structure of analysed populations may have biased the assessed AAO of bipolar disorder, contributing to the observed differences. Although prior research has identified AAO differences across continents (for example the incidence of early-onset bipolar disorder is higher in the USA than in Europe)[30] this study is the first to systematically assess this heterogeneity across many cohorts with different ascertainment strategies.

For the polarity at disease onset, the relative proportion of patients reporting a depressive index episode did not differ across continents but across instruments. A (hypo)manic onset was more common if the onset was based on an impairment/help-seeking instead of diagnostic interview phenotype definition.

Phenotypic heterogeneity affects genetic analyses

Interestingly, the systematic differences in AAO phenotypes across cohorts are reflected in heritability estimates: we observed the highest SNV-based heritability h^2_{SNV} when onset was established by diagnostic interview and the lowest when it was captured with more health system-specific and subjective measurements, such as item 4 of the Operational Criteria Checklist for Psychotic Illness (impairment/help-seeking). Moreover, h^2_{SNV} estimates approached zero when all samples were combined in our primary analysis ($h^2_{SNV} = 0.05$; 95% CI 0–0.12), underscoring the strong impact of phenotypic heterogeneity. For PAO-M/-X versus PAO-D, we observed significant h^2_{SNV} estimates, demonstrating that genetic factors contribute to the polarity at bipolar disorder onset.

Thus, we not only showed systematic heterogeneity in a clinically relevant psychiatric phenotype across cohorts but also provided direct evidence for how this heterogeneity can hamper genetic studies. Similarly, a recent investigation demonstrated that the phenotyping method (for example diagnostic interview versus self-report) significantly influenced heritability estimates, GWAS results and PGS performance in analyses of major depression susceptibility, with broader phenotype definitions resulting in lower heritability estimates.[31] These results indicate that although increasing samples sizes generally improves the power to detect significant associations, larger samples are no silver bullet: careful phenotype harmonisation and uniform recruitment strategies are likely at least as important.

Limitations

In addition to diverse phenotype definitions originating from different ascertainment methods, as described above, several factors may have limited the cross-cohort comparability of the AAO and PAO. These factors include differences in the definition and ascertainment of the age at bipolar disorder onset and in how bipolar disorder was diagnosed across cohorts and continents. Such differences can lead to bias, affecting genetic analyses. For example, as patients diagnosed with bipolar disorder type II show, on average, later ages at onset than patients with bipolar disorder type I,[32] differing proportions of bipolar disorder subtypes across cohorts may have an impact on AAO analyses. Therefore, we included the bipolar disorder subtype as a covariate in our genetic analyses to control for this confounder. Still, this cross-cohort heterogeneity has likely reduced our statistical power.

Given that, for all included cohorts, the disease onset phenotypes were assessed retrospectively, measurement errors associated with interrater reliabilities and recall bias may have occurred across cohorts. For example, hypomania was likely underreported, potentially biasing the PAO towards depression. Notably, such potential issues are not specific to the present study but may affect all retrospective analyses of psychiatric phenotypes. Nevertheless, differences in the diagnosis of bipolar disorder and the ascertained phenotypes between cohorts might have exacerbated these problems. Therefore, future studies should focus on compiling clinically more homogeneous, phenotypically better-harmonised data-sets instead of only assembling the largest possible sample.

Furthermore, the rank-based inverse normal transformation of the AAO phenotype may have affected the GWAS and heritability analyses. We conducted this transformation because, first, the original AAO distribution was highly skewed and thus not suitable for linear regression and, second, the AAO differed significantly between cohorts, which could have biased the meta-analysis. However, by transforming the data, only the rank and not the absolute differences in onset between patients was maintained, reducing the interpretability of the phenotype and the genetic effects.

We performed both SNV-level and polygenic score associations using a structured meta-analysis, which mitigates some of the noise introduced by phenotypic heterogeneity. However, we were unable to account for differences in the underlying genetic aetiology of the phenotypes across cohorts. As described above, phenotypic heterogeneity is an important limitation of our study and should be considered in future phenotype and genetic analyses. Our results need to be interpreted in light of these limitations.

Implications

Phenotypes of bipolar disorder onset are clinically important trait measures contributing to the well-known clinical and biological heterogeneity of this severe psychiatric disorder. Genetic analysis of AAO and PAO may lead to a better understanding of the biological risk factors underlying mental illness and support clinical assessment and prediction. Our study provides evidence of a genetic contribution to age and polarity at bipolar disorder onset but also demonstrates the need for systematic harmonisation of clinical data on bipolar disorder onset in future studies.

Janos L. Kalman, MD, Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Germany; Department of Psychiatry and Psychotherapy, University Hospital Munich, Germany; and International Max Planck Research School for Translational Psychiatry, Germany; **Loes M. Olde Loohuis**, PhD, Center for Neurobehavioral Genetics, Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles, USA; **Annabel Vreeker**, PhD, Department of Child and Adolescent Psychiatry/Psychology, Erasmus University Medical Centre–Sophia Children's Hospital, the Netherlands; **Andrew McQuillin**, PhD, Division of Psychiatry, University College London, UK; **Eli A. Stahl**, PhD, Division of Psychiatric Genomics, Mount Sinai School of Medicine, USA; **Douglas Ruderfer**, PhD, Division of Genetic Medicine, Department of Medicine, Vanderbilt Genetics Institute, Vanderbilt University Medical Center, USA; Department of Biomedical Informatics, Vanderbilt University Medical Center, USA; and Department of Psychiatry and Behavioral Sciences, Vanderbilt University Medical Center, USA; **Maria Grigoroiu-Serbanescu**, PhD, Alexandru Obregia Clinical Psychiatric Hospital, Bucharest, Romania; **Georgia Panagiotaropoulou**, MSc, Department of Psychiatry and Psychotherapy, Charite – Universitätsmedizin, Germany; **Stephan Ripke**, MD, PhD, Analytic and Translational Genetics Unit, Massachusetts General Hospital, USA; and Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, USA; **Tim B. Bigdeli**, PhD, Department of Psychiatry and Behavioral Sciences, SUNY Downstate Health Sciences University, USA; and VA NY Harbor Healthcare System, USA; **Frederike Stein**, MA, Department of Psychiatry and Psychotherapy, Philipps-University Marburg, Germany; **Tina Meller**, Dr rer nat, MSc, Department of Psychiatry and Psychotherapy, Philipps-University Marburg, Germany; and Center for Mind, Brain and Behavior (CMBB), Germany; **Susanne Meinert**, MSc, Institute for Translational Psychiatry, Westfälische Wilhelms-Universität Münster, Germany; and Institute for Translational Neuroscience, University of Münster, Germany; **Helena Pelin**, MSc, International Max Planck Research School for Translational Psychiatry, Germany; and Max Planck Institute of Psychiatry, Germany; **Fabian Streit**, PhD, Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Germany; **Sergi Papiol**, PhD, Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Germany; Department of Psychiatry and Psychotherapy, University Hospital Munich, Germany; and Centro de Investigación Biomedica en Red de Salud Mental (CIBERSAM), Spain; **Mark J. Adams**, PhD, Division of Psychiatry, University of Edinburgh, UK; **Rolf Adolfsson**, MD, PhD, Department of Clinical Sciences, Medical Faculty, Umeå University, Sweden; **Kristina Adorjan**, MD, Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Germany; and Department of Psychiatry and Psychotherapy, University Hospital Munich, Germany; **Ingrid Agartz**, MD, PhD, Department of Clinical Neuroscience, Centre for Psychiatry Research, Karolinska Institutet, Sweden; Department of Psychiatric Research, Diakonhjemmet Hospital, Norway; and NORMENT Centre, Division of Mental Health and

Addiction, Institute of Clinical Medicine, University of Oslo, Norway; **Sofie R. Aminoff**, PhD, Division of Mental Health and Addiction, Oslo University Hospital, Norway; and NORMENT Centre, Inst of Clinical Medicine, University of Oslo, Norway; **Heike Anderson-Schmidt**, Dipl-Psych, Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Germany; **Ole A. Andreassen**, MD, PhD, NORMENT Centre, Inst of Clinical Medicine, University of Oslo, Norway; and Division of Mental Health and Addiction, Oslo University Hosptial, Norway; **Raffaella Ardau**, MD, Unit of Clinical Pharmacology, University Hospital Agency of Cagliari, Italy; **Jean-Michel Aubry**, MD, Faculty of medicine, University of Geneva, Switzerland; and Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt, Germany; **Ceylan Balaban**, MScm, Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt, Germany; **Nicholas Bass**, MRCPsych, Division of Psychiatry, University College London, UK; **Bernhard T. Baune**, MD, PhD, Department of Psychiatry, University of Münster, Germany; Department of Psychiatry, Melbourne Medical School, The University of Melbourne, Australia; The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Australia; and Discipline of Psychiatry, Adelaide Medical School, The University of Adelaide, Australia; **Frank Bellivier**, MD, PhD, Universite de Paris, France; INSERM UMRS 1144, France; and DMU Neurosciences, GHU Lariboisière Fernand Widal, Departement de Psychiatrie, APHP, France; **Antoni Benabarre**, MD, PhD, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Spain; **Susanne Bengesser**, MD, PhD, Department of Psychiatry and Psychotherapeutic Medicine, Medical University Graz, Austria; **Wade H Berrettini**, MD, PhD, Psychiatry, University of Pennsylvania, USA; **Marco P. Boks**, MD, PhD, Psychiatry, UMC Utrecht Brain Center, the Netherlands; **Evelyn J. Bromet**, PhD, Department of Psychiatry, Stony Brook University, USA; **Katharina Brosch**, MSc, Department of Psychiatry and Psychotherapy, Philipps-University Marburg, Germany; **Monika Budde**, PhD, Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Germany; **William Byerley**, MD, Psychiatry, University of California San Francisco, USA; **Pablo Cervantes**, MD, Department of Psychiatry, McGill University, Canada; **Catina Chillotti**, MD, Unit of Clinical Pharmacology, University Hospital Agency of Cagliari, Italy; **Sven Cichon**, PhD, Department of Biomedicine, University of Basel, Switzerland; Institute of Human Genetics, University of Bonn, School of Medicine & University Hospital Bonn, Germany; Institute of Medical Genetics and Pathology, University Hospital Basel, Switzerland; and Institute of Neuroscience and Medicine (INM-1), Research Centre Julich, Germany; **Scott R. Clark**, MD, PhD, Discipline of Psychiatry, University of Adelaide, Australia; and Bazil Hetzel Institute, Australia; **Ashley L. Comes**, PhD, Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Germany; Department of Psychiatry and Psychotherapy, University Hospital Munich, Germany; and International Max Planck Research School for Translational Psychiatry, Germany; **Aiden Corvin**, MD, PhD, Department of Psychiatry & Trinity Translational Medicine Institute, Trinity College Dublin, Ireland; **William Coryell**, MD, University of Iowa Hospitals and Clinics, USA; **Nick Craddock**, MD, Medical Research Council Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, UK; **David W. Craig**, PhD, Translational Genomics, USC, USA; **Paul E. Croarkin**, DO, MS, Department of Psychiatry and Psychology, Mayo Clinic, USA; **Cristiana Cruceanu**, PhD, Department of Translational Research, Max Planck Institute of Psychiatry, Germany; **Piotr M. Czerski**, PhD, Department of Psychiatric Genetics, Poznan University of Medical Sciences, Poland; **Nina Dalkner**, PhD, Department of Psychiatry and Psychotherapeutic Medicine, Medical University Graz, Austria; **Udo Dannlowski**, MD, PhD, Institute for Translational Psychiatry, Westfälische Wilhelms-Universität Münster, Germany; **Franziska Degenhardt**, MD, Institute of Human Genetics, University of Bonn, School of Medicine & University Hospital Bonn, Germany; and Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital Essen, University of Duisburg-Essen, Germany; **Maria Del Zompo**, MD, Department of Biomedical Science, Section of Neuroscience & Clinical Pharmacology, University of Cagliari, Italy; and Unit of Clinical Pharmacology, University Hospital Agency of Cagliari, Italy; **J. Raymond DePaulo**, MD, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, USA; **Srdjan Djurovic**, PhD, Department of Medical Genetics, Oslo University Hospital Ullevål, Norway; and NORMENT, Department of Clinical Science, University of Bergen, Norway; **Howard J. Edenberg**, PhD, Department of Biochemistry and Molecular Biology, Indiana University School of Medicine, USA; **Mariam Al Eissa**, PhD, Division of Psychiatry, University College London, UK; **Torbjørn Elvsåshagen**, MD, PhD, NORMENT, Division of Mental Health and Addiction, Oslo University Hospital, Norway; **Bruno Etain**, MD, PhD, Universite de Paris, France; INSERM UMRS 1144, France; and DMU Neurosciences, GHU Lariboisière Fernand Widal, Departement de Psychiatrie, APHP, France; **Ayman H. Fanous**, MD, Department of Psychiatry and Behavioral Sciences, SUNY Downstate Health Sciences University, USA; and VA NY Harbor Healthcare System, USA; **Frederike Fellendorf**, MD, Department of Psychiatry and Psychotherapeutic Medicine, Medical University Graz, Austria; **Alessia Fiorentino**, PhD, Division of Psychiatry, University College London, UK; **Andreas J. Forstner**, MD, Institute of Human Genetics, University of Bonn, School of Medicine & University Hospital Bonn, Germany; and Centre for Human Genetics, University of Marburg, Germany; **Mark A. Frye**, MD, Department of Psychiatry and Psychology, Mayo Clinic, USA; **Janice M. Fullerton**, PhD, Neuroscience Research Australia, Australia; and School of Medical Sciences, University of New South Wales, Australia; **Katrin Gade**, MD, Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Germany; **Julie Garnham**, BN, RN, Nova Scotia Health Authority, Canada; **Elliot Gershon**, MD, Department of Psychiatry and Behavioral Neuroscience, University of Chicago, USA; and Department of Human Genetics, University of Chicago, USA; **Michael Gill**, MD, Department of Psychiatry & Trinity Translational Medicine Institute, Trinity College Dublin, Ireland; **Fernando S. Goes**, MD, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, USA; **Katherine Gordon-Smith**, PhD, Psychological Medicine, University of Worcester, UK; **Paul Grof**, MD, PhD, Mood Disorders Centre of Ottawa, Canada; and Department of Psychiatry, University of Toronto, Canada; **Jose Guzman-Parra**, PhD, Mental Health Department, University Regional Hospital, Biomedicine Institute (IBIMA), Spain; **Tim Hahn**, PhD, Institute for Translational Psychiatry, Westfälische Wilhelms-Universität Münster, Germany; **Roland Hasler**, PhD, Cell Biology, SUNY Downstate Medical Center College of Medicine, USA; and Institute for Genomic Health, SUNY Downstate Medical Center College of Medicine, USA; **Maria Heilbronner**, Dipl-Psych, Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Germany; **Urs Heilbronner**, PhD, Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Germany; **Stephane Jamain**, PhD, Universite Paris Est Creteil, France; and INSERM U 955, Neuropsychiatrie Translationnelle, France; **Esther Jimenez**, MSc, PhD, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Spain; **Ian Jones**, PhD, MD, Medical Research Council Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, UK; **Lisa Jones**, PhD, Psychological Medicine, University of Worcester, UK; **Lina Jonsson**, MSc, Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg, Sweden; **Rene S. Kahn**, MD, PhD, Department of Psychiatry, Icahn School of Medicine at Mount Sinai, USA; **John R. Kelsoe**, MD, Department of Psychiatry, University of California San Diego, USA; **James L. Kennedy**, MD, Department of Psychiatry, University of Toronto, Canada; The Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Canada; and Institute of Medical Science, University of Toronto, Canada; **Tilo Kircher**, MD, Department of Psychiatry and Psychotherapy, Philipps-University Marburg, Germany; **George Kirov**, PhD, MD, Medical Research Council Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, UK; **Sarah Kittel-Schneider**, MD, Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt, Germany; and Department of Psychiatry, Psychotherapy and Psychosomatics, University Hospital Wurzburg, Germany; **Farah Klöhn-Saghatolislam**, MD, MBA, Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Germany; **James A. Knowles**, MD, PhD, Cell Biology, SUNY Downstate Medical Center College of Medicine, USA; and Institute for Genomic Health, SUNY Downstate Medical Center College of Medicine, USA; **Thorsten M. Kranz**, PhD, Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt, Germany; **Trine Vik Lagerberg**, PhD, NORMENT Centre, Division of Mental Health and Addiction, Oslo University Hosptial, Norway; **Mikael Landen**, MD, PhD, Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg, Sweden; and Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Sweden; **William B. Lawson**, MD, Department of Psychiatry and Behavioral Sciences, Howard University Hospital, USA; **Marion Leboyer**, MD, PhD, Universite Paris Est Creteil, France; and INSERM U 955, Neuropsychiatrie Translationnelle, France; **Qingqin S. Li**, PhD, Neuroscience, Janssen Research & Development, USA; **Mario Maj**, MD, PhD, Department of Psychiatry, University of Campania 'Luigi Vanvitelli', Italy; **Dolores Malaspina**, MD, MS, MSPH, Department of Psychiatry, Icahn School of Medicine at Mount Sinai, USA; and Department of Genetics & Genomics, Icahn School of Medicine at Mount Sinai, USA; **Mirko Manchia**, MD, PhD, Unit of Psychiatry, Department of Medical Sciences and Public Health, University of Cagliari, Italy and Department of Pharmacology, Dalhousie University, Canada; **Fermin Mayoral**, PhD, MDF, Mental Health Department, University Regional Hospital, Biomedicine Institute (IBIMA), Spain; **Susan L. McElroy**, MD, Research Institute, Lindner Center of HOPE, USA; **Melvin G. McInnis**, MD, Department of Psychiatry, University of Michigan, USA; **Andrew M. McIntosh**, MD, FRCPsych, Division of Psychiatry, University of Edinburgh, UK; **Helena Medeiros**, MSW, LICSW, Institute for Genomic Health, SUNY Downstate Medical Center College of Medicine, USA; **Ingrid Melle**, MD, PhD, NORMENT Centre, Division of Mental Health and Addiction, Institute of Clinical Medicine and Diakonhjemmet Hospital, University of Oslo, Norway; and Division of Mental Health and Addiction, Oslo University Hospital, Norway; **Vihra Milanova**, MD, PhD, Psychiatric Clinic, Alexander University Hospital, Bulgaria; **Philip B. Mitchell**, MD, School of Psychiatry, University of New South Wales, Australia; **Palmiero Monteleone**, MD, Department of Medicine, Surgery and Dentistry 'Scuola Medica Salernitana', University of Salerno, Italy; **Alessio Maria Monteleone**, MD, Department of Psychiatry, University of Campania 'Luigi Vanvitelli', Italy; **Markus M. Nöthen**, MD, Institute of Human Genetics, University of Bonn, School of Medicine & University Hospital Bonn, Germany; **Tomas Novak**, PhD, National Institute of Mental Health, Czech Republic; **John I. Nurnberger**, MD, PhD, Psychiatry, Indiana University School of Medicine, USA; **Niamh O'Brien**, PhD, Division of Psychiatry, University College London, UK; **Kevin S. O'Connell**, PhD, Division of Mental Health and Addiction, Oslo University Hospital, Norway; and NORMENT Centre, Inst of Clinical Medicine, University of Oslo, Norway; **Claire O'Donovan**, MB, BchBAO, Department of Psychiatry, Dalhousie University, Canada; **Michael C. O'Donovan**, PhD, MD, Medical Research Council Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, UK; **Nils Opel**, MD, Institute for Translational Psychiatry, Westfälische Wilhelms-Universität Münster, Germany; **Abigail Ortiz**, MD, MSc, FRCPC, Department of Psychiatry, University of Toronto, Toronto, Canada; and Centre for Addiction and Mental Health, Toronto, Canada; **Michael J. Owen**, PhD, MD, Medical Research Council Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, UK; **Erik Pålsson**, PhD, Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg, Sweden; **Carlos Pato**, MD, PhD, Institute for Genomic Health, SUNY Downstate Medical Center College of Medicine, USA; **Michele T. Pato**, MD, Institute for Genomic Health, SUNY Downstate Medical Center College of Medicine, USA; **Joanna Pawlak**, PhD, MD, Department of Psychiatric Genetics, Poznan University of Medical Sciences, Poland; **Julia-Katharina Pfarr**, MSc, Department of Psychiatry and Psychotherapy, Philipps-University Marburg, Germany; **Claudia Pisanu**, MD, Department of Biomedical Science, Section of Neuroscience & Clinical Pharmacology, University of Cagliari, Italy; **James B. Potash**, MD, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, USA; **Mark H Rapaport**, MD, Department of Psychiatry and Behavioral Sciences, Emory University, USA; **Daniela Reich-Erkelenz**, MA, Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Germany; **Andreas Reif**, MD, Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt, Germany; **Eva Reininghaus**, MD, PhD, Department of Psychiatry and Psychotherapeutic Medicine, Medical University Graz, Austria; **Jonathan Repple**, MD, Institute for Translational Psychiatry, Westfälische Wilhelms-Universität Münster, Germany; **Hélène Richard-Lepouriel**, MD, Department of Psychiatry, Geneva University Hospitals, Switzerland; **Marcella Rietschel**, MD, Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Germany; **Kai Ringwald**, MSc, Department of Psychiatry and Psychotherapy, Philipps-University Marburg, Germany; **Gloria Roberts**, PhD, School of Psychiatry, University of New South Wales, Australia; **Guy Rouleau**, MD, PhD, FRCPC, FRSC, Montreal Neurological Institute, Canada and Department of Neurology, McGill University,

Canada; **Sabrina Schaupp**, MSc, Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Germany; **William A Scheftner**, MD, Department of Psychiatry, Rush Medical College, USA; **Simon Schmitt**, MSc, Department of Psychiatry and Psychotherapy, Philipps-University Marburg, Germany; **Peter R. Schofield**, PhD DSc, Neuroscience Research Australia, Australia; and School of Medical Sciences, University of New South Wales, Australia; **K. Oliver Schubert**, MD, PhD, Discipline of Psychiatry, University of Adelaide, Australia; and Northern Adelaide Mental Health Service, SA Health, Australia; **Eva C. Schulte**, MD, PhD, Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Germany; and Department of Psychiatry and Psychotherapy, University Hospital Munich, Germany; **Barbara Schweizer**, RN, BS, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, USA; **Fanny Senner**, MD, Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Germany; and Department of Psychiatry and Psychotherapy, University Hospital Munich, Germany; **Giovanni Severino**, MD, Department of Biomedical Science, Section of Neuroscience & Clinical Pharmacology, University of Cagliari, Italy; **Sally Sharp**, PhD, Division of Psychiatry, University College London, UK; **Claire Slaney**, RN, Nova Scotia Health Authority, Canada; **Olav B. Smeland**, MD, PhD, Division of Mental Health and Addiction, Oslo University Hospital, Norway; and NORMENT Centre, Inst of Clinical Medicine, University of Oslo, Norway; **Janet L. Sobell**, PhD, Psychiatry and the Behavioral Sciences, University of Southern California, USA; **Alessio Squassina**, Ph.D. MSci, Department of Psychiatry, Dalhousie University, Canada; and Department of Biomedical Science, Section of Neuroscience & Clinical Pharmacology, University of Cagliari, Italy; **Pavla Stopkova**, PhD, National Institute of Mental Health, Czech Republic; **John Strauss**, MD, Department of Psychiatry, University of Toronto, Canada; The Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Canada; and Institute of Medical Science, University of Toronto, Canada; **Alfonso Tortorella**, PhD, Department of Psychiatry, University of Perugia, Italy; **Gustavo Turecki**, MD, PhD, Department of Psychiatry, McGill University, Canada; and Douglas Institute, McGill University, Canada; **Joanna Twarowska-Hauser**, MD, PhD, Department of Psychiatric Genetics, Poznan University of Medical Sciences, Poland; **Marin Veldic**, MD, Department of Psychiatry and Psychology, Mayo Clinic, USA; **Eduard Vieta**, MD, PhD, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Spain; **John B. Vincent**, PhD, Department of Psychiatry, University of Toronto, Canada; The Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Canada; and Institute of Medical Science, University of Toronto, Canada; **Wei Xu**, PhD, Dalla Lana School of Public Health, Biostatistics Division, University of Toronto, Canada; **Clement C. Zai**, PhD, Department of Psychiatry, University of Toronto, Canada; The Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Canada; Institute of Medical Science, University of Toronto, Canada; Laboratory Medicine and Pathobiology, University of Toronto, Canada; and Harvard T.H. Chan School of Public Health, USA; **Peter P. Zandi**, MHS, MPH, PhD, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, USA; **Psychiatric Genomics Consortium (PGC) Bipolar Disorder Working Group**; **International Consortium on Lithium Genetics (ConLiGen)**; **Colombia-US Cross Disorder Collaboration in Psychiatric Genetics**; **Arianna Di Florio**, MD, PhD, MD, Medical Research Council Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, UK; **Jordan W. Smoller**, MD, ScD, Psychiatric and Neurodevelopmental Genetics Unit, Department of Psychiatry and Center for Genomic Medicine, Massachusetts General Hospital, USA; and Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, USA; **Joanna M. Biernacka**, PhD, Department of Psychiatry and Psychology, Mayo Clinic, USA; and Department of Health Sciences Research, Mayo Clinic, USA; **Francis J. McMahon**, MD, Human Genetics Branch, Intramural Research Program, National Institute of Mental Health, USA; **Martin Alda**, MD, National Institute of Mental Health, Czech Republic; and Department of Psychiatry, Dalhousie University, Canada; **Bertram Müller-Myhsok**, MD, Max Planck Institute of Psychiatry, Germany; **Nikolaos Koutsouleris**, MD, Department of Psychiatry and Psychotherapy, University Hospital Munich, Germany; Max Planck Institute of Psychiatry, Germany; and Institute of Psychiatry, Psychology and Neuroscience, Kings College London, UK; **Peter Falkai**, MD, Department of Psychiatry and Psychotherapy, University Hospital Munich, Germany; **Nelson B. Freimer**, MD, Center for Neurobehavioral Genetics, Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles, USA; and Human Genetics, University of California Los Angeles, USA; **Till F.M. Andlauer**, PhD, Department of Neurology, Klinikum rechts der Isar, School of Medicine, Technical University of Munich, Germany; **Thomas G. Schulze**, MD, Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Germany; Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Germany; Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Germany; Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, USA; and Department of Psychiatry and Behavioral Sciences, SUNY Upstate Medical University, USA; **Roel A. Ophoff**, PhD, Center for Neurobehavioral Genetics, Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles, USA; Human Genetics, University of California Los Angeles, USA; and Psychiatry, Erasmus University Medical Center, the Netherlands

Correspondence: Janos L. Kalman. Email: janos.kalman@med.uni-muenchen.de; Loes M. Olde Loohuis. Email: loldeloohuis@mednet.ucla.edu

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Supplementary material

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Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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Author contributions

Concept and design: Janos L. Kalman, Loes M. Olde Loohuis, Annabel Vreeker, Till F.M. Andlauer, Thomas G. Schulze and Roel A. Ophoff. Analysis and interpretation of data: Janos L. Kalman, Loes M. Olde Loohuis, Annabel Vreeker and Till F.M. Andlauer. Drafting of the manuscript: Janos L. Kalman, Loes M. Olde Loohuis, Annabel Vreeker and Till F.M. Andlauer. Supervision, and critical revision of the manuscript: Thomas G. Schulze, Roel A. Ophoff, Francis J. McMahon, Jordan W. Smoller and Martin Alda. All other authors provided data, contributed ideas and suggestions for analyses, interpreted results and revised the final manuscript.

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Supplementary Material

Table of contents

Description of the individual study samples

The list below provides a detailed description (based on the original publications (1,2)) of all cohorts that were part of the present study.

1. Discovery samples

ume4* | *Sweden
Clinical characterization of the patients included the Mini-International Neuropsychiatric Interview (MINI), Diagnostic Interview for Genetic Studies (DIGS), Family Interview for Genetic Studies (FIGS), and Schedules for Clinical Assessment in Neuropsychiatry (SCAN). The final diagnoses were made according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) and determined by consensus of 2 research psychiatrists.

hal2* | *Canada
The case samples were recruited from patients longitudinally followed at specialty mood disorders clinics in Halifax and Ottawa (Canada). Cases were interviewed in a blind fashion with the Schedule of Affective Disorders and Schizophrenia-Lifetime version (SADS-L), and consensus diagnoses were made according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) and Research Diagnostic Criteria (RDC). Protocols and procedures were approved by the local ethics committees, and written informed consent was obtained from all patients before participation in the study.

top7* | *Norway
In the TOP study (Thematically Organized Psychosis research), patients of European ancestry who were born in Norway were recruited from psychiatric hospitals in the Oslo region. Patients were diagnosed according to the Structured Clinical Interview (SCID) for DSM-IV. All participants provided written informed consent, and the Norwegian Scientific-Ethical Committee and the Norwegian Data Protection Agency approved the protocol.

top8* | *Norway
The TOP8 bipolar disorder (BD) patients were recruited in the same way as the top7 cohort described above and recruited from hospitals across Norway.

may1* | *USA
Cases of BD were drawn from the Mayo Clinic Bipolar Biobank. Enrolment sites included Mayo Clinic, Rochester, Minnesota; Lindner Center of HOPE/University of Cincinnati College of Medicine, Cincinnati, Ohio; and the University of Minnesota, Minneapolis, Minnesota. Enrolment at each site was approved by the local institutional review board (IRB), and all participants had consented to use of their data for future genetic studies. Participants were identified through routine clinical appointments, among inpatients in mood disorder units, and by recruitment advertising. They were required to be between 18 and 80 years old, be able to speak English and provide informed consent and have DSM-IV-TR diagnostic confirmation of BD-I or BD-II or schizoaffective bipolar disorder, as determined with the SCID.

edi1 | UK
This sample comprised Caucasian individuals contacted through the inpatient and outpatient services of hospitals in southeast Scotland. A BD-I diagnosis was based on an interview with the patient with the SADS-L, supplemented by case note review and frequently by information from medical staff, relatives, and caregivers. Final diagnoses, which were based on DSM-IV criteria, were reached by consensus between 2 trained psychiatrists. The study was approved by the Multi-Centre Research Ethics Committee for Scotland, and patients gave written informed consent for the collection of DNA samples for use in genetic studies.

ageu |Sweden
The patients with BD were identified in the Swedish National Quality Register for Bipolar Disorders (BipoläR) and the Swedish National Patient Register (with a validated algorithm that required at least 2 hospitalizations with a BD diagnosis). A confirmatory telephone interview with a diagnostic review was conducted. Additional patients were recruited from the St. Göran Bipolar Project (Affective Center at Northern Stockholm Psychiatry Clinic, Sweden), which enrolled new and ongoing patients diagnosed with BD by using structured clinical interviews. Diagnoses were made according to the DSM-IV (BipoläR and St. Göran Bipolar Project) and ICD-10 criteria (National Patient Register). All recruitment procedures were approved by the Regional EthicaBl Committees in Sweden.

auom | Australia
For the current analysis, datasets from the following study sites were combined and analyzed together:
Adelaide subsample (n = 58): Patients were collected as part of "The Cognitive Function and Mood Study (CoFaM-Study)," which was conducted at the Discipline of Psychiatry, University of Adelaide, Australia. Patients were diagnosed with the MINI diagnostic interview version 6.0. These diagnoses were compared with medical records and, for consistency reasons, the final clinical diagnosis was made following to DSM-IV criteria. The study was approved by ethics committees of the University of Adelaide and the Royal Adelaide Hospital. All participants provided written informed consent before study procedures were performed.
Sydney subsample (n = 27): Patients were recruited at the Mood Disorder Unit, Prince of Wales Hospital, in Sydney. All patients received a lifetime diagnosis of BD according to the DSM-IV criteria on the basis of a consensus best-estimate procedure and structured diagnostic interviews with the DIGS, FIGS, and SCID. Study protocols were reviewed and approved in advance by the IRBs of the participating institutions. All patients provided written informed consent.

euo2 | Italy
Patients were recruited among outpatients attending the Department of Psychiatry at the University of Campania “Luigi Vanvitelli” in Naples. All patients received a lifetime diagnosis of BD according to the DSM-IV criteria on the basis of a consensus best-estimate procedure that considered all available information, including the Structured Clinical Interview for DSM-IV Disorders (SCID-I)–Patient Edition (SCID-IP), medical records, and a routine clinical interview. In addition, psychopathological rating scales and the retrospective chart of the National Institute of Mental Health Life Chart Method were used for detailed and longitudinal assessment of clinical aspects of BD. The

study was approved by the local IRB. All participants provided written informed consent.

euol | Italy

The sample comprised 181 unrelated patients with BD I. All patients were of Sardinian ancestry for at least 3 generations. They were recruited at the outpatient unit (Lithium Clinic) of the Clinical Psychopharmacology Center at the Department of Biomedical Science, Section of Neuroscience & Clinical Pharmacology, University of Cagliari, Cagliari, Italy, and Unit of Clinical Pharmacology, University Hospital Agency of Cagliari, Cagliari, Italy. Lifetime consensus diagnoses according to RDC were made by trained clinical psychopharmacologists on the basis of data from a personal semi-structured interview and a systematic review of patients' medical records. Informed written consent to participate in the study was obtained from all patients. The study was approved by the local ethics committee.

euoR | Austria, Czech Republic, France, Germany, Romania, Spain, Switzerland, Sweden

For the current analysis, datasets from the following study sites were combined and analyzed together:

Austrian subsample (n = 35): Patients were recruited at the Medical University of Graz, Department of Psychiatry and Psychotherapeutic Medicine. All patients received a lifetime diagnosis of BD according to the DSM-IV criteria on the basis of a consensus best-estimate procedure that considered all available information, including structured diagnostic interviews with the SCID, medical records, and personal medical history. Study protocols were reviewed and approved in advance by the IRBs of the participating institutions. All participants provided written informed consent.

Czech subsample (n = 45): Unrelated patients were recruited in in- and outpatient units at the Prague Psychiatric Center, Psychiatric Hospital Bohnice, Psychiatric Clinic, Czech Republic. Diagnoses were made on the basis of either a SADS-L interview or on an unstructured clinical interview modified from SADS-L by using RDC criteria. All patients signed an informed consent form approved by the IRBs of the Prague Psychiatric Center.

French subsample (n = 46): The research sample comprised participants recruited between 1995 and 2008 from 3 university-affiliated departments of psychiatry (Paris, Bordeaux, and Nancy) in France. The inclusion criteria were that the individual (a) was aged 18 years or older; (b) had a mood disorder that met DSM-IV criteria for BD-I or BD-II or BD not otherwise specified (BDNOS); (c) currently met criteria for euthymia, which was operationalized as scores below 5 on both the Montgomery-Åsberg Depression Rating Scale and the Bech Mania Rating Scale; and (d) was willing and able to give written informed consent. Study protocols were reviewed and approved by the IRBs of the participating institutions. Patients meeting the above inclusion criteria were assessed by psychiatrists trained in the use of the French version of the DIGS.

German subsample (n = 71): Patients were recruited from consecutive admissions to psychiatric inpatient units at the University Hospital Würzburg. All patients received a lifetime diagnosis of BD according to the DSM-IV criteria on the basis of a consensus best-estimate procedure that considered all available information, including semi-structured diagnostic interviews using the Association for Methodology and Documentation in Psychiatry (AMDP), medical records, and the family history method. In addition, the Operational Criteria Checklist for Psychotic Illness (OPCRIT) was used

for detailed polydiagnostic documentation of symptoms. Study protocols were reviewed and approved in advance by the IRBs of the participating institutions. All patients provided written informed consent.

Romanian subsample (n = 8): Patients who had taken lithium for at least 2 years (lithium treatment response evaluated with the Retrospective Criteria of Long-Term Treatment Response in Research Subjects with Bipolar Disorder [Alda scale]) were recruited from consecutive admissions to the Obregia Clinical Psychiatric Hospital, Bucharest, Romania. Patients were interviewed with the DIGS and FIGS. Information was also obtained from medical records and close relatives. The diagnosis of BD-I was assigned according to DSM-IV criteria by using the best estimate procedure. Patients were included in the sample if they had at least 2 documented hospitalizations for illness episodes (1 manic/mixed and 1 depressive or 2 manic episodes). All participants provided written informed consent. The study was performed in accordance with the ethical principles of the Declaration of Helsinki.

Spanish subsample (n = 73): Cases were recruited from the Bipolar Disorder Program of the Hospital Clinic of Barcelona and Mental Health Services from Oviedo, under the umbrella of the Spanish Research Network on Mental Health (CIBERSAM). Participants were selected only if they fulfilled the following inclusion criteria: (i) met DSM-IV-TR criteria for BD-I or -II, (ii) age over 18 years, (iii) met criteria for euthymia for at least 3 months before inclusion, assessed by the Hamilton Depression Rating Scale (HDRS) and the Young Mania Rating Scale (YMRS), and (iv) provided both written and verbal informed consent. Exclusion criteria were as follows: (i) intelligence quotient (IQ) lower than 70, (ii) the presence of any medical condition affecting neuropsychological performance, and (iii) electroconvulsive therapy within the past year. The study was approved by each institution's ethics committees and was performed in accordance with the ethical principles of the Declaration of Helsinki.

Swedish subsample (n = 80): The patients with BD were identified in the Swedish National Quality Register for Bipolar Disorders (BipoläR) and the Swedish National Patient Register (with a validated algorithm that required at least 2 hospitalizations with a BD diagnosis). A confirmatory telephone interview with a diagnostic review was conducted. Additional patients were recruited from the St. Göran Bipolar Project (Affective Center at Northern Stockholm Psychiatry Clinic, Sweden), which enrolled new and ongoing patients diagnosed with BD by using structured clinical interviews. Diagnoses were made according to the DSM-IV (BipoläR and St. Göran Bipolar Project) and ICD-10 criteria (National Patient Register). All recruitment procedures were approved by the Regional Ethical Committees in Sweden.

Swiss subsample (n = 52): Patients with BD were recruited in the specialized outpatient unit for mood disorders at the Division of Psychiatric Specialties of the Department of Psychiatry in Geneva. Patients are referred to this unit by psychiatrists or general practitioners for diagnostic assessment and care. Individuals diagnosed by a trained psychiatrist or clinical psychologist with a DSM-IV diagnosis of BD-I or -II were included in this study. Clinical and anamnestic data (medical histories, family history, onset of the disorder, and previous treatments) were collected during the interview. Patients with BD were evaluated with the French version of the DIGS or the French version of the SCID (SCID I, version 2.0). They were also evaluated for comorbid Axis I disorders with the DIGS. Treatment response to lithium was evaluated with the Alda scale. All patients completed self-report questionnaires, including the Barrat Impulsiveness Scale (BIS-10), State Anger Expression Inventory (STAXI), Beck Hopelessness Scale (BHS), Childhood Trauma Questionnaire (CTQ), Brown-

Goodwin Aggression Scale (BGA) and the Geneva Suicide History Form. All patients provided written informed consent.

h66x| Germany, Poland

For the current analysis, datasets from the following study sites were combined and analyzed together:

Polish subsample (n = 88): Patients were recruited at the Department of Psychiatry, Poznan University of Medical Sciences, Poznan, Poland. All patients received a lifetime diagnosis of BD according to the DSM-IV criteria on the basis of a consensus best-estimate procedure and structured diagnostic interviews with the SCID. Study protocols were reviewed and approved in advance by the IRBs of the participating institutions. All subjects provided written informed consent.

German subsample (n = 4): Patients were recruited from consecutive admissions to the in- and outpatient units of the Department of Psychiatry and Psychotherapy at the Universities of Dresden and Berlin (Charité), Germany. DSM-IV lifetime diagnoses of BD-I were assigned on the basis of a consensus best-estimate procedure that considered all available information, including a structured interview with the SCID and medical records. Study protocols were reviewed and approved in advance by the IRBs of the participating institutions. All patients provided written informed consent.

naom | USA

For the current analysis, datasets from the following study sites were combined and analyzed together:

Baltimore subsample (n = 11): Patients were recruited at the Johns Hopkins Hospital in Baltimore, Maryland, USA. All patients received a lifetime diagnosis of BD-I according to the DSM-IV criteria on the basis of a consensus best-estimate procedure that considered all available information, including structured diagnostic interviews with the Diagnostic Interview for Genetic Studies, medical records, and the family history method. Study protocols were reviewed and approved in advance by the IRB of the Johns Hopkins Hospital. All patients provided written informed consent.

Iowa City subsample (n = 13): Patients were recruited at the University of Iowa Hospitals and Clinics in Iowa City, Iowa, USA. All patients received a lifetime diagnosis of BD-I according to the DSM-IV criteria on the basis of a consensus best-estimate procedure that considered all available information, including structured diagnostic interviews with the DIGS, medical records, and the family history method. Study protocols were reviewed and approved in advance by the IRB of the University of Iowa, Carver College of Medicine. All patients provided written informed consent.

NIMH subsample (n = 17): Patients were recruited in the same way as those in the gain cohort. Study protocols were reviewed and approved in advance by the IRBs of the participating institutions. All patients provided written informed consent.

Rochester subsample (n = 26): Cases of BD were drawn from the Mayo Clinic Bipolar Biobank. Enrolment sites included Mayo Clinic, Rochester, Minnesota; Lindner Center of HOPE/University of Cincinnati College of Medicine, Cincinnati, Ohio; and the University of Minnesota, Minneapolis, Minnesota. Enrolment at each site was approved by the local IRB, and all participants had consented to the use of their data in future genetic studies. Participants were identified through routine clinical appointments, among inpatients admitted in mood disorder units, and by recruitment advertising. Participants were required to be between 18 and 80 years old and be able to speak English and provide informed consent and have DSM-IV-TR diagnostic

confirmation of BD-I or -II or schizoaffective bipolar disorder, as determined with the SCID.
San Diego subsample (n = 92): Patients were recruited from individuals at the University of California, San Diego, as described for the gain samples below.

dub1* | *Ireland
Samples were collected as part of a larger study on the genetics of psychotic disorders in the Republic of Ireland, under protocols approved by the relevant IRBs and with written informed consent that permitted repository use. Patients were recruited from hospitals and community psychiatric facilities in Ireland by a psychiatrist or psychiatric nurse trained in using the SCID. Diagnosis was based on the structured interview and supplemented by case note review and collateral history, where available. All diagnoses were reviewed by an independent reviewer.

wtccc* | *United Kingdom
Patients were all over the age of 17 years, living in the UK, and of European descent. Recruitment was undertaken throughout the UK and included individuals who had been in contact with mental health services and had a lifetime history of high mood. After providing written informed consent, participants were interviewed by a trained psychologist or psychiatrist with a semi-structured lifetime diagnostic psychiatric interview (SCAN) and available psychiatric medical records were reviewed. On the basis of all available data, best-estimate life-time diagnoses were made according to the RDC. In the current study, we included cases with a lifetime diagnosis of RDC BD-I, BD-II, or schizoaffective disorder, bipolar type. All patients were recruited under protocols approved by the appropriate IRBs and gave written informed consent.

bmau* | *Australia
Patients were recruited at the Mood Disorder Unit, Prince of Wales Hospital in Sydney. All patients received a lifetime diagnosis of BD according to the DSM-IV criteria on the basis of a consensus best-estimate procedure and structured diagnostic interviews with the DIGS, FIGS, and SCID. Study protocols were reviewed and approved in advance by the IRBs of the participating institutions. All patients provided written informed consent.

rom3* | *Romania
Patients with BD-I (n = 233) were recruited from consecutive admissions to the Obregia Clinical Psychiatric Hospital, Bucharest, Romania. Patients were interviewed with the DIGS and FIGS. Information was also obtained from medical records and close relatives. The diagnosis of BD-I was assigned according to DSM-IV criteria on the basis of the best estimate procedure. All patients had at least 2 hospitalizations for illness episodes. All participants provided written informed consent. The study was performed in accordance with the ethical principles of the Declaration of Helsinki.

bmpo* | *Poland
Patients were recruited at the Department of Psychiatry, Poznan University of Medical Sciences, Poznan, Poland. All patients received a lifetime diagnosis of BD according to the DSM-IV criteria on the basis of a consensus best-estimate procedure and structured diagnostic interviews with the SCID. Study protocols were reviewed and approved in advance by the IRBs of the participating institutions. All patients provided written informed consent.

gain | USA

Genetic Association Information Network (GAIN)/ The Bipolar Genome Study (BiGS)

The BD sample was collected under the auspices of the NIMH Genetics Initiative for BD (http://zork.wustl.edu/nimh/), genotyped as part of GAIN and analyzed as part of a larger GWAS conducted by the BiGS consortium. Approximately half of the GAIN sample was collected as multiplex families or sib-pair families (waves 1-4), and the remainder was collected as individual cases (wave 5). Patients were recruited at 11 sites: Indiana University; John Hopkins University; the NIMH Intramural Research Program; Washington University at St. Louis; University of Pennsylvania; University of Chicago; Rush Medical School; University of Iowa; University of California, San Diego; University of California, San Francisco; and University of Michigan. All investigations were carried out after the review of protocols by the IRB at each participating institution. At all sites, potential patients were identified from screening admissions to local treatment facilities and through publicity programs or advocacy groups and evaluated with the DIGS, FIGS, and information from relatives and medical records. All information was reviewed through a best-estimate diagnostic procedure by 2 independent and non-interviewing clinicians and a best-estimate diagnosis was reached. In the event of a disagreement, a third review was performed to break the tie.

tgco2 | USA

Patients were recruited from individuals at the 11 US sites described for the GAIN sample as part of FAT2, FaST, BiGS, and TGEN cohorts. Eligible participants were aged 18 or older and met DSM-IV criteria for BD-I or BD-II by consensus diagnosis based on interviews with the Affective Disorders Evaluation (ADE) and MINI. All participants provided written informed consent, and the study protocol was approved by the IRB at each site. Collection of phenotypic data and DNA samples was supported by NIMH grants MH063445 (JW Smoller); MH067288 (PI: P Sklar), MH63420 (PI: V Nimgaonkar), and MH078151, MH92758 (PI: J. Kelsoe). The samples were independent of those included in the GAIN sample.

butr | Bulgaria

All patients were recruited in Bulgaria from psychiatric inpatient and outpatient services. Each patient had a history of hospitalization and was interviewed with an abbreviated version of the SCAN. Consensus best-estimate diagnoses were made by 2 researchers according to DSM-IV criteria. All participants gave written informed consent, and the study was approved by local ethics committees at the participating centers.

swa2 | Sweden

The patients with BD were identified in the Swedish National Quality Register for Bipolar Disorders (BipoläR) and the Swedish National Patient Register (with a validated algorithm that required at least two hospitalizations with a BD diagnosis). A confirmatory telephone interview with a diagnostic review was conducted. Additional patients were recruited from the St. Göran Bipolar Project (Affective Center at Northern Stockholm Psychiatry Clinic, Sweden), which enrolled new and ongoing patients diagnosed with BD with structured clinical interviews. Diagnoses were made according to the DSM-IV (BipoläR and St. Göran Bipolar Project) and ICD-10 criteria (National Patient Register). All recruitment procedures were approved by the Regional Ethical Committees in Sweden.

fran | France
Patients with BD-I or BD-II were recruited as part of a large study on the genetics of BD in France (Paris-Creteil, Bordeaux, Nancy) with a protocol approved by the relevant IRBs and with written informed consent. Patients were of French descent for more than 3 generations and were assessed by a trained psychiatrist or psychologist with structured interviews, supplemented by medical case notes, mood scales, and a self-rating questionnaire that assessed dimensions.

uclo | United Kingdom
The UCL sample comprised Caucasian individuals who were recruited by and received clinical diagnoses of BD-I from UK National Health Service (NHS) psychiatrists at interview on the basis of the criteria of the ICD-10. In addition, patients with BD were included only if both parents were of English, Irish, Welsh, or Scottish descent and if 3 out of 4 grandparents were of the same descent. All patients read an information sheet approved by the Metropolitan Medical Research Ethics Committee, which also approved the project for all NHS hospitals. Written informed consent was obtained from each patient.

bonn | Germany
Patients for the BOMA-Bipolar Study were recruited from consecutive admissions to the inpatient units of the Department of Psychiatry and Psychotherapy at the University of Bonn and the Central Institute for Mental Health in Mannheim, University of Heidelberg, Germany. DSM-IV lifetime diagnoses of BD-I were assigned on the basis of a consensus best-estimate procedure that considered all available information, including a structured interview with the SCID and SADS-L, medical records, and the family history method. In addition, the OPCRIT checklist was used for the detailed polydiagnostic documentation of symptoms. Study protocols were reviewed and approved in advance by the IRBs of the participating institutions. All patients provided written informed consent.

bmg2 | Germany
Patients were recruited from consecutive admissions to psychiatric inpatient units at the University Hospital Würzburg. All patients received a lifetime diagnosis of BD according to the DSM-IV criteria on the basis of a consensus best-estimate procedure that considered all available information, including semi-structured diagnostic interviews with the AMDP, medical records, and the family history method. In addition, the OPCRIT system was used for the detailed polydiagnostic documentation of symptoms. Study protocols were reviewed and approved in advance by the IRBs of the participating institutions. All patients provided written informed consent.

bmg3 | Germany
Patients were recruited at the Central Institute of Mental Health in Mannheim, University of Heidelberg, and other collaborating psychiatric hospitals in Germany. All patients received a lifetime diagnosis of BD according to the DSM-IV criteria on the basis of a consensus best-estimate procedure that considered all available information, including structured diagnostic interviews with the AMDP, Composite International Diagnostic Screener (CID-S), SADS-L, and/or SCID, medical records, and the family history method. In addition, the OPCRIT system was used for the detailed polydiagnostic documentation of symptoms. Study protocols were reviewed

and approved in advance by the IRBs of the participating institutions. All patients provided written informed consent.

bmsp | Spain
Patients were recruited at the mental health departments of the following 5 centers in Andalusia, Spain: University Hospital Reina Sofia of Córdoba, Provincial Hospital of Jaen; Hospital of Jerez de la Frontera (Cádiz); Hospital of Puerto Real (Cádiz); Hospital Punta Europa of Algeciras (Cádiz); and Hospital Universitario San Cecilio (Granada). Diagnoses were made on the basis of the SADS-L, OPCRIT, a review of medical records, and interviews with first- and/or second-degree family members with the Family Informant Schedule and Criteria (FISC). Consensus best-estimate BD diagnoses were assigned by 2 or more independent senior psychiatrists and/or psychologists and according to the RDC and DSM-IV. Study protocols were reviewed and approved in advance by the IRBs of the participating institutions. All patients provided written informed consent.

ucla | Netherlands
The case sample consisted of in- and outpatients recruited through psychiatric hospitals and institutions throughout the Netherlands. Patients with DSM-IV BD, determined after interview with the SCID, were included in the analysis. Ethical approval was provided by UCLA and local ethics committees, and all participants gave written informed consent.

usc2 | USA
Genomic Psychiatry Consortium (GPC) patients were recruited via the University of Southern California healthcare system. Diagnoses were based on DSM-IV-TR criteria and were established with the OPCRIT on the basis of a combination of focused, direct interviews and data extracted from medical records.

mich | USA
The Pritzker Neuropsychiatric Disorders Research Consortium (NIMH/Pritzker) patients were from the NIMH Genetics Initiative Genetics Initiative Repository. Patients were diagnosed according to DSM-III or DSM-IV criteria by diagnostic interviews and/or medical record reviews. Cases with low confidence diagnoses were excluded. From each non-Ashkenazi European-origin family available from wave 1-5, 2 siblings with BD-I were included, when possible, and the patients was preferentially included, if possible (n = 946 individuals in 473 sibling pairs); otherwise, a single patient with BD-I was included (n = 184). The sibling pairs with BD were retained within the NIMH/Pritzker sample when individuals in more than 1 study were uniquely assigned to a study set.

stp1 | USA
The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) was a 7-site, national US, longitudinal cohort study designed to examine the effectiveness of treatments and their impact on the course of BD. The study enrolled 4361 participants who met DSM-IV criteria for BD-I, BD-II, BDNOS, schizoaffective manic or bipolar type, or cyclothymic disorder on the basis of diagnostic interviews. From the parent study, 2089 individuals with BD-I or -II diagnoses who were over 18 years of age consented to the collection of blood samples for DNA. BD samples with a consensus diagnosis of BD-I were selected for inclusion in STEP1.

m&m's | Germany, Austria
PsyCourse subsample (n = 365): The samples form part of a multi-site German/Austrian longitudinal study (www.psycourse.de).(3) Diagnoses were made according to DSM-IV. Study protocols were reviewed and approved in advance by the IRBs of the participating institutions. All patients provided written informed consent. The current analyses are based on the v3.1. version of the data set.
FOR2017 subsample (n = 88): In- and outpatients (aged 18-65) were recruited as part of an ongoing multi-center (Universities of Marburg and Münster, Germany) cohort study (DFG research group FOR2107, www.for2107.de). Trained psychologists conducted semi-structured interviews for DSM-IV axis I disorders (SCID-I). The study protocols were approved by the ethics committees of the Medical Schools of the Universities of Marburg and Münster, following the Declaration of Helsinki, and all participants provided written informed consent.

2. Replication samples

bdtrs | Germany
The Bipolar Disorder Treatment Response Study (BP-TRS) comprises inpatients with BD and screened controls of Caucasian background. A trained psychologist or psychiatrist conducted a face-to-face interview with SCID or MINI 6.0 to ascertain the presence of BD according to DSM-IV criteria. Patients aged 18 years and older were included if a current or lifetime diagnosis of BD was determined in this structured diagnostic interview. Other assessments, including symptom ratings, psychiatric history, treatment history, and treatment response, were based on an interview by trained psychologists/psychiatrists. All patients provided written informed consent.

ukwa1 | United Kingdom
The UCL sample comprised Caucasian individuals who were recruited by and received clinical diagnoses of BD-I from UK National Health Service (NHS) psychiatrists at interview on the basis of the criteria of the ICD-10. In addition, patients with BD were included only if both parents were of English, Irish, Welsh, or Scottish descent and if 3 out of 4 grandparents were of the same descent. All volunteers read an information sheet approved by the Metropolitan Medical Research Ethics Committee, which also approved the project for all NHS hospitals. Written informed consent was obtained from each volunteer.

dutch | Netherlands
The case sample consisted of in- and outpatients recruited through psychiatric hospitals and institutions throughout the Netherlands. Patients with DSM-IV BD, determined after interview with the SCID, were included in the analysis. Ethical approval was provided by UCLA and local ethics committees, and all participants gave written informed consent.

bmrom | Romania
The sample *bmrom* (N = 225 BD-I cases) also included patients from the ConLiGen-Romania sample who did not overlap with the Romanian PGC2 sample bip_rom3_eur. Patients with BD-I were recruited from consecutive admissions in the Obregia Psychiatric Hospital of Bucharest, Romania. Patients were interviewed with the DIGS and FIGS. Information was also obtained from medical records and close relatives. The diagnosis of BD-I was assigned according to DSM-IV criteria by the best estimate

procedure. Patients were included in the sample if they had at least 2 documented hospitalizations for illness episodes (1 manic/mixed and 1 depressive or 2 manic episodes). All participants provided written informed consent. The study was performed in accordance with the ethical principles of Declaration of Helsinki. Patients in the ConLiGen-Romania study were recruited in the same manner as the other patients in the ***bmrom*** sample and were required to have taken lithium for at least 2 years; lithium treatment response was evaluated with the Alda scale.

jst5* | *USA

The study included unrelated patients with BD-I from 6 clinical trials (IDs: NCT00253162, NCT00257075, NCT00076115, NCT00299715, NCT00309699, and NCT00309686). Janssen Research & Development, LLC (formerly known as Johnson & Johnson Pharmaceutical Research & Development, LLC) recruited participants to assess the efficacy and safety of risperidone. Patients were diagnosed with BD according to DSM-IV-TR criteria. The diagnosis of BD was confirmed by the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) in NCT00076115, by the SCID in NCT00257075 and NCT00253162, and by the MINI in NCT00299715, NCT00309699, and NCT00309686. Additional detailed descriptions of these clinical trials can be found at ClinicalTrials.gov. Only patients of European ancestry were included in the current analysis.

col1* | *Colombia

Patients with BD-I and -II were recruited as part of a larger cohort of patients with severe mental illness through psychiatric hospitals in the Paisa region of Colombia. Protocols and procedures were approved by the local and UCLA ethics committees, and written informed consent was obtained from all patients before participation in the study. Phenotyping included diagnostic interview (NetSCID-5, Spanish version), additional assessments of individual symptoms, and a neurocognitive battery.

Supplementary Methods

Phenotype analyses: Statistical analysis

We analyzed the relationship of age at onset and polarity at onset with disease characteristics only in patients with BD-I. To optimize comparability between studies, we dichotomized the following variables: lifetime delusions, lifetime hallucinations, suicidal ideation, suicide attempt, educational attainment, current smoking, and living together with a partner (all variables were dichotomized as yes/no except for educational attainment, which was dichotomized as lower/higher; see Supplementary Table S9). We considered the number of manic and depressive episodes as continuous variables. However, to adjust for illness duration we calculated the frequency of episodes per year as: ((number of episodes) / (years of illness + 1)). Then, we rank-normalized these variables for analysis.

We analyzed the associations of age at onset and polarity at onset with dichotomous illness characteristics by logistic regression analysis. The various dichotomous illness characteristics were used as the outcome, and either age at onset or polarity at onset was used as the determinant. In addition, we analyzed the associations of age at onset and polarity at onset with the frequency of episodes per year by separate linear regression analyses. Sex was included as a covariate in all analyses. Regression analyses were performed in SPSS 25.0. Results from both datasets were then combined by a fixed-effects meta-analysis in R (package Metafor). We applied the Bonferroni-Holm method to correct for multiple testing.

Supplementary Notes

Supplementary Note S1. References to published methods

Method / Tool	Reference
PGC Rapid Imputation and Computational Pipeline for GWAS (RICOPILI)	Lam et al. 2020 (4)
SHAPEIT	Delaneau et al. 2013 (5)
IMPUTE2	Howie et al. 2009, Howie et. al 2012 (6,7)
PLINK	Purcell et al. 2007, Chang et al. 2015 (8,9)
METAL	Willer et al. 2010 (10)
PRS-CS	Ge et al. 2019 (11)
GCTA GREML	Yang et al. 2010, Yang et al. 2011 (12,13)
LDSC (Linkage disequilibrium score regression)	Bulik-Sullivan et al. 2015 (14)

Supplementary Note S2. Secondary phenotype analyses

Since our finding that a later AAO was associated with a higher frequency of episodes per year of illness were contrary to previous findings in other studies (Etain *et al.*), we conducted secondary analyses in which we used the normalized age at onset and gender as predictors and the untransformed number of episodes (not controlled for years of illness) as outcome variables. The distribution of the residuals of these models did not follow a normal distribution. Therefore, these results should be interpreted with caution.

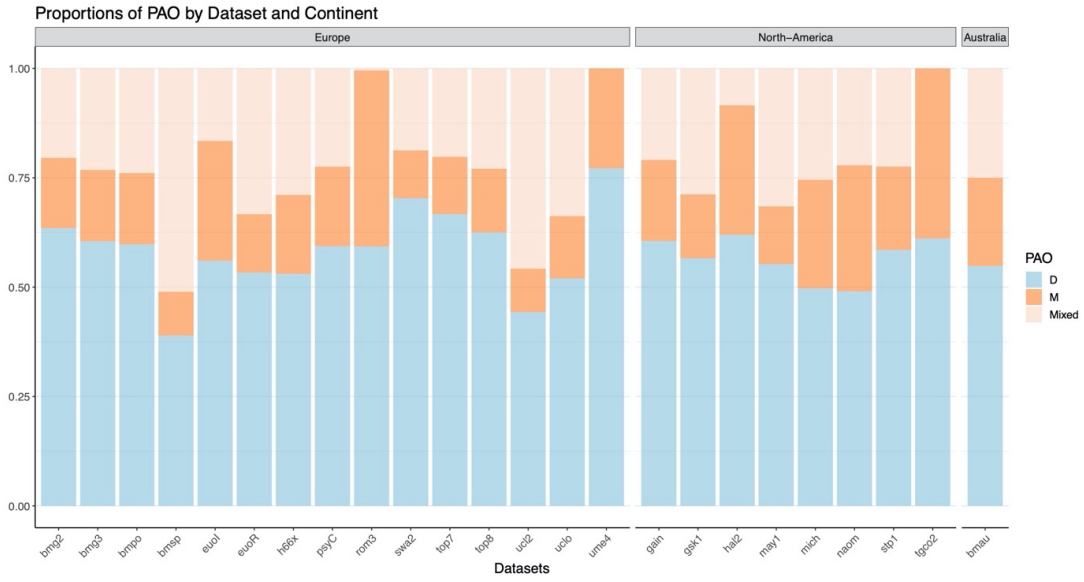
In the Dutch study, the association of the age at onset with less manic episodes was not significant (β=-0.41, SE=0.25, $p=1.01\times10^{-1}$). However, a later age at onset was significantly associated with fewer depressive episodes (β=-1.04, SE=0.41, $p=1.03\times10^{-2}$). In the German dataset, a later age at onset was significantly associated with fewer manic (β=-1.48, SE=0.46, $p=1.35\times10^{-3}$) and depressive episodes (β=-2.04, SE=0.56, $p=3.72\times10^{-4}$).

Supplementary Figures

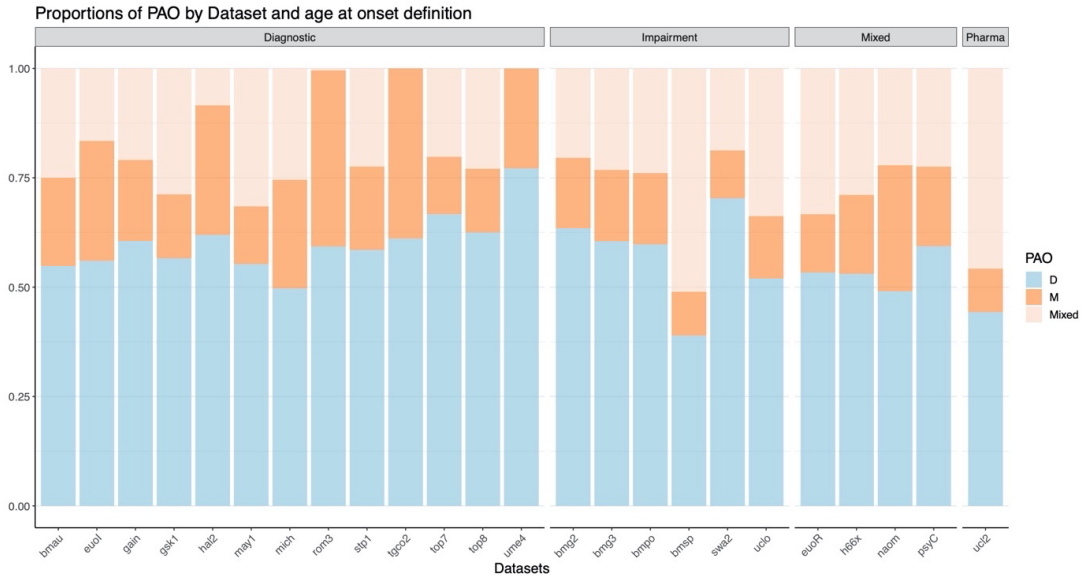
Supplementary Figure S1. Proportions of each category of polarity at onset by continent and definition of age at onset

Categories of polarity at onset (PAO): D, depression before mania/hypomania; M, mania/hypomania before depression; Mixed, mixed episodes or first manic and depressive episode in same year.

A: Proportions of PAO by dataset and continent

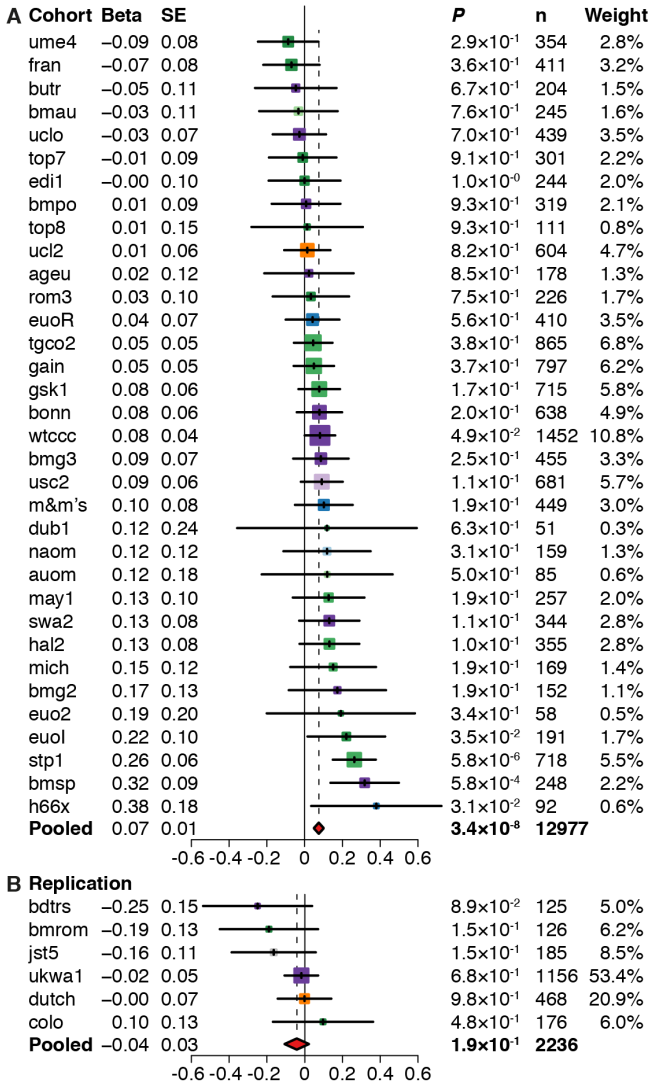


B: Proportions of PAO by dataset and definition of age at onset



Supplementary Figure S2. Forest plots from the GWAS on age at onset

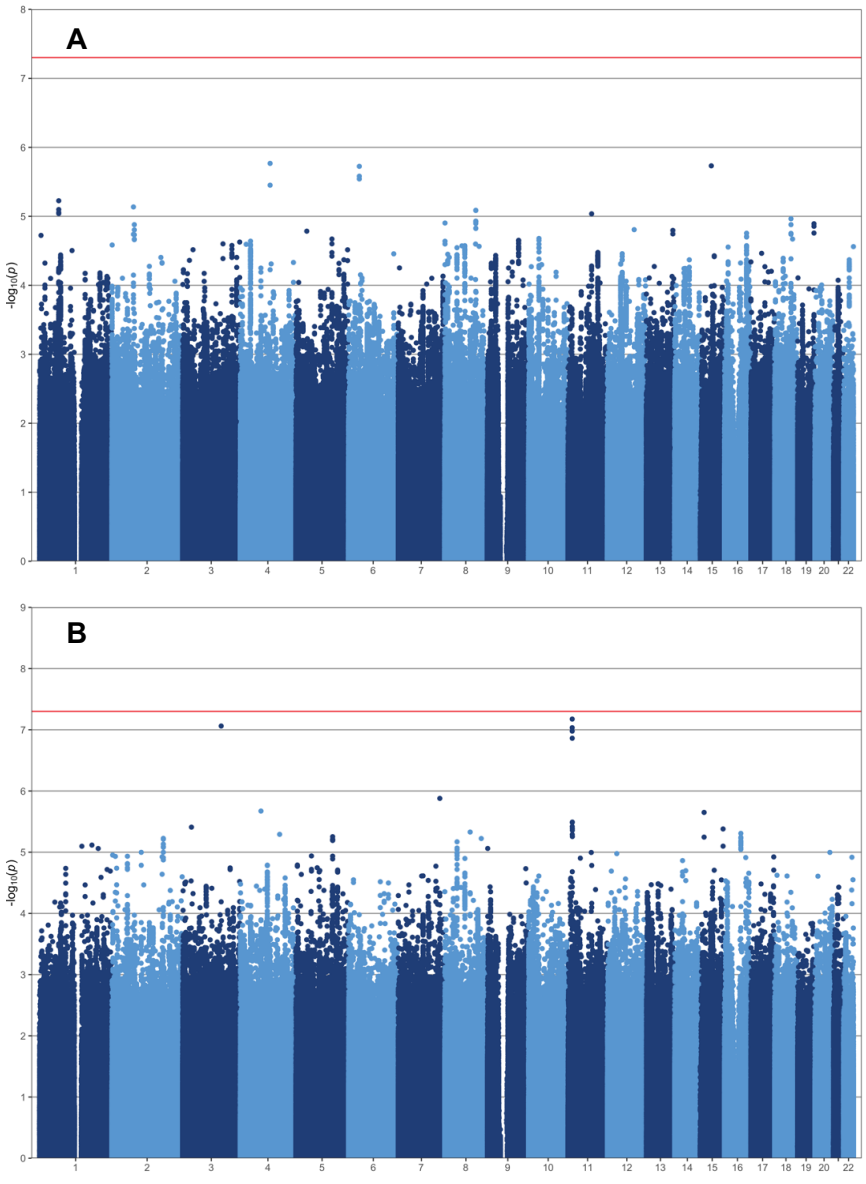
A: Forest plot of the results of the discovery-stage analysis of the top-associated variant rs1610275. The effect size beta is relative to the minor allele G. The color scheme corresponds to the colors used in Fig. 1
B: Forest plot of the results of the replication-stage analysis of variant rs1610275



Supplementary Figure S3. Results of the GWAS on polarity at onset

A: Manhattan plot of the primary PAO (PAO-M/-X [n=2888] *vs.* PAO-D [n=3885]) GWAS
B: Manhattan plot of the secondary PAO (PAO-M [n=1350] *vs.* PAO-D [n=3599]) GWAS

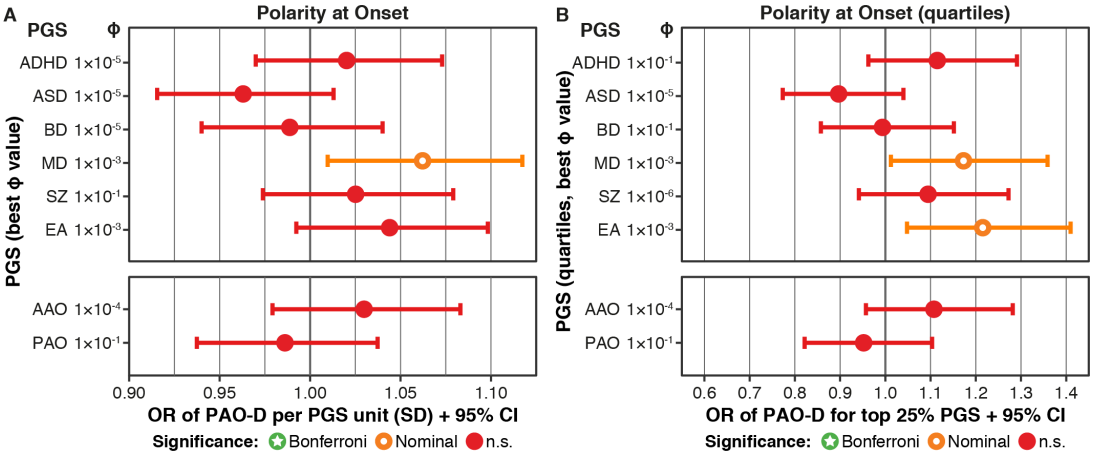
Abbreviations: PAO-M, mania/hypomania before depression; PAO-X, mixed episodes or first manic and depressive episode in same year; PAO-D, depression before mania/hypomania.



Supplementary Figure S4: Results from analyses of polygenic scores with the polarity of onset

A: Associations of polygenic scores (PGSs) with the polarity at onset (PAO-M and PAO-X *vs.* PAO-D). A higher odds ratio (OR) thus indicates an association with PAO-D.
B: Associations of the PAO (PAO-M and PAO-X *vs.* PAO-D) with the top *vs.* bottom PGS quartiles. A higher OR indicates an association with PAO-D.

Significance levels: n.s., *P*>0.05; Nominal, *P*<0.05; Bonferroni, below the Bonferroni-corrected significance threshold corrected for 96 tests (*P*<5.2×10-4).
For detailed results, see Supplementary Table S8.
Abbreviations: ADHD, attention deficit/hyperactivity disorder; ASD, autism spectrum disorder; MD, major depression; SZ, schizophrenia; EA, educational attainment; PAO-M, mania/hypomania before depression; PAO-X, mixed episodes or first manic and depressive episode in same year; PAO-D, depression before mania/hypomania.



Supplementary Tables

Supplementary Table S1. Overview of the definitions of age at onset (AAO) used by the individual cohorts and their mapping to AAO definition groups in the present manuscript

Stage	Dataset	Definition of AAO used by the cohort	AAO definition
Discovery	**wtccc**	Age (years) at first impairment due to an episode of depression, hypomania, mania, or mixed affective episode.	Impairment / help-seeking
	tgco2	Age at which the patient first met DSM-IV criteria for a manic, mixed, or major depressive episode.	Diagnostic interview
	gain	Age at which proband reported first manic, mixed, or major depressive episode.	Diagnostic interview
	stp1	Age at which the patient first met DSM-IV criteria for a manic, mixed, or major depressive episode.	Diagnostic interview
	gsk1	Age at which the patient first experienced manic or depressive symptoms, as reported by the patient during the interview	Diagnostic interview
	usc2	Age at which psychiatric treatment was first sought or symptoms first began to cause subjective distress or impair functioning, whichever occurred first.	Impairment / help-seeking
	bonn	Age at which psychiatric treatment was first sought or symptoms first began to cause subjective distress or impair functioning, whichever occurred first.	Impairment / help-seeking
	ucl2	Age at which the patient first received medication to treat a depressive/hypomanic/manic episode	Pharmacotherapy
	bmg3	Age at which psychiatric treatment was first sought or symptoms first began to cause subjective distress or impair functioning, whichever occurred first.	Impairment / help-seeking
	m&m's	*PsyCourse (n = 365):* Age at which the patient experienced the first (hypo)manic or depressive episode, based on SCID.	Mixed

Stage	Dataset	Definition of AAO used by the cohort	AAO definition
		FOR 2107 (n = 88): Age at which psychiatric treatment was first sought or when symptoms first began to cause subjective distress or impair functioning, whichever occurred first.	
	uclo	Age at which psychiatric treatment was first sought or when symptoms first began to cause subjective distress or impair functioning, whichever occurred first.	Impairment / help-seeking
	fran	Age at which the patient was first reliably diagnosed with a major mood episode (major depression, (hypo)mania, or mixed episode) according to the appropriate section of the DIGS	Diagnostic interview
	euoR	*Austria (n = 35):* Age at first subjective symptoms. *Czech Republic (N = 45):* Age at first illness episode. *France (n = 46):* Age at which the patient was first reliably diagnosed with a major mood episode (major depression, (hypo)mania or mixed episode) according to the appropriate section of the DIGS. *Romania (n = 8):* Age at which the patient first met DSM-IV criteria for a manic, mixed, or major depressive episode. *Spain (n = 73):* Age at which the patient first met DSM-IV criteria for a manic, mixed, or major depressive episode. *Germany (n = 71):* First contact with mental health services because of depressive or manic symptoms. *Sweden (n = 80):* How old were you when you had your first health care contact for these disorders? *Switzerland (n = 52):* Age at which the patient first met diagnostic criteria for a manic, mixed, or major depressive episode.	Mixed
	hal2	Age at which the patient first met DSM-IV criteria for a manic, mixed, or major depressive episode.	Diagnostic interview
	ume4	Age at first ever symptoms of depression, hypomania, or mania on the basis of semi-structured clinical interviews and/or information from clinical records and close relatives.	Diagnostic interview
	swa2	How old were you when you had your first health care contact for these disorders?	Impairment / help-seeking

Stage	Dataset	Definition of AAO used by the cohort	AAO definition
	bmpo	Age at which psychiatric treatment was first sought or when symptoms first began to cause subjective distress or impair functioning, whichever occurred first.	Impairment / help-seeking
	top7	Age at which the patient first met DSM-IV criteria for a manic, mixed, or major depressive episode.	Diagnostic interview
	may1	Age at which the patient first met DSM-IV criteria for a manic, mixed, or major depressive episode.	Diagnostic interview
	bmsp	Age at which psychiatric treatment was first sought or when symptoms first began to cause subjective distress or impair functioning, whichever occurred first.	Impairment / help-seeking
	bmau	Age at which the patient first met DSM-IV criteria for a manic, mixed, or major depressive episode.	Diagnostic interview
	edi1	Recorded as SADS-L items: Age when patient first met criteria for BD	Diagnostic interview
	rom3	Age at which the patient first met DSM-IV criteria for a manic, mixed, or major depressive episode.	Diagnostic interview
	butr	Age at first impairment caused by symptoms	Impairment / help-seeking
	euol	The first reliably diagnosed (hypo)manic or depressive episode according to RDC criteria, determined by using all available medical records	Diagnostic interview
	ageu	How old were you when you had your first health care contact for these disorders?	Impairment / help-seeking
	mich	Age at which the patient first met DSM-IV criteria for a manic, mixed, or major depressive episode.	Diagnostic interview
	naom	*NIMH (n = 17):* unknown *Rochester (n = 26):* Age at which the patient first met DSM-IV criteria for a manic, mixed, or major depressive episode. *Iowa City (n = 13):* Age (self-reported) at which the patient first met the diagnostic criteria for a manic or depressive episode. *Baltimore (n = 11):* Age (self-reported) at which the patient first met the diagnostic criteria for a manic or depressive episode.	Mixed

Stage	Dataset	Definition of AAO used by the cohort	AAO definition
		San Diego (n = 92): Age at which the patient first met DSM-IV criteria for a manic, mixed, or major depressive episode.	
	bmg2	First contact with mental health services because of depressive or manic symptoms.	Impairment / help-seeking
	top8	Age at which the patient first met DSM-IV criteria for a manic, mixed, or major depressive episode.	Diagnostic interview
	h66x	*Poland (n = 88):* Age at which psychiatric treatment was first sought OR symptoms first began to cause subjective distress or impair functioning, whichever occurred first. *Germany (n = 4):* Age at which the patient experienced the first (hypo)manic, mixed or depressive episode, based on SCID.	Mixed
	auom	*Adelaide (n = 58):* Age at which the patient first met DSM-IV criteria for a manic, mixed, or major depressive episode. *Sydney (n = 27):* Age at which the patient first met DSM-IV criteria for a manic, mixed, or major depressive episode.	Diagnostic interview
	euo2	Age at which the patient first met the DSM criteria for a mood episode.	Diagnostic interview
	dub1	Age at which the patient first met DSM-IV criteria for a manic, mixed, or major depressive episode.	Diagnostic interview
Replication	**ukwa1**	Age at which psychiatric treatment was first sought or symptoms first began to cause subjective distress or impair functioning, whichever occurred first.	Impairment / help-seeking
	dutch	Age at which the patient first received medication to treat a (hypo)manic, mixed or depressive episode.	Pharmacotherapy
	jst5	Unknown	Unknown
	colo	Age at which the patient experienced the first (hypo)manic or depressive episode, based on SCID.	Diagnostic interview
	bmrom	Age at which the patient first met DSM-IV criteria for a manic, mixed, or major depressive episode.	Diagnostic interview
	bdtrs	Age at which psychiatric treatment was first sought	Impairment / help-seeking

Supplementary Table S2. Overview of the genotyping panels and variant counts across the different cohorts used in the primary analyses of age at onset (AAO) and polarity at onset (PAO)

Stage	Dataset	N	Array	No. of variants before imputation	No. of variants in AAO GWAS	No. of variants in AAO meta	AAO GWAS λ	No. of variants in PAO meta	PAO GWAS λ
Discovery	**wtccc**	1452	A5.0	432 682	8 801 813	7 398 963	1.017		
	tgco2	865	A6.0	563 959	8 798 153	7 563 915	1.005	7 405 389	0.972
	gain	797	A6.0	677 788	8 820 816	7 591 369	0.998	7 429 600	0.986
	stp1	718	A5.0	331 202	8 806 379	7 498 623	0.997	7 355 792	0.985
	gsk1	715	I550	528 201	8 865 282	7 715 207	0.999	7 546 691	0.992
	usc2	681	OMEX	598 185	8 985 804	7 701 214	1.007		
	bonn	638	I550	499 494	8 815 645	7 589 780	0.984		
	ucl2	604	OMEX	611 804	8 818 599	7 589 780	1.009	7 497 908	0.998
	bmg3	455	I550, I610Q, I660Q	456 677	8 822 557	7 589 780	1.000	7 258 756	1.005
	m&m's	449	PsychChip	244 756	8 793 857	7 411 897	0.995	7 208 612	0.986
	uclo	439	A5.0	344 528	8 759 835	7 351 105	1.005	7 178 838	0.995
	fran	411	I650	279 572	8 788 132	7 342 980	1.003		
	euoR	410	OMEX	624 675	8 922 825	7 617 456	1.003		
	hal2	355	OMEX	566 260	8 848 629	7 612 730	1.000	7 387 863	1.002
	ume4	354	OMEX	632 614	8 957 109	7 612 730	1.007	7 330 826	0.975
	swa2	344	A6.0	518 940	8 851 757	7 557 815	1.01		
	bmpo	319	I317, I660Q	269 263	8 738 828	7 557 815	1.005	7 190 724	1.021
	top7	301	A6.0	667 707	8 893 696	7 616 405	1.005		
	may1	257	OMEX	686 229	8 867 638	7 618 138	1.000	7 350 084	1.005
	bmsp	248	I610Q. I660Q	329 661	9 080 402	7 476 861	1.003	7 303 425	1.01
	bmau	245	I660Q	505 360	8 788 122	7 623 983	1.014	7 293 919	1.004
	edi1	244	A5.0	344 775	8 741 391	7 344 672	1.008		

Stage	Dataset	N	Array	No. of variants before imputation	No. of variants in AAO GWAS	No. of variants in AAO meta	AAO GWAS λ	No. of variants in PAO meta	PAO GWAS λ
	rom3	226	OMEX	587 509	8 910 533	7 570 414	0.997	7 337 453	1.005
	butr	204	OMEX	656 165	8 978 379	7 659 546	0.993		
	euol	191	OMEX	622 541	8 954 061	7 264 673	1.016	6 974 295	1.031
	ageu	178	A6.0	494 795	9 065 654	7 635 983	0.999		
	mich	169	I550	509 425	8 824 078	7 575 360	1.009	7 328 734	1.027
	naom	159	OMEX	624 553	8 898 168	7 600 346	0.996	7 090 346	1.034
	bmg2	152	I01Q	789 442	8 828 658	7 561 747	1.001		
	top8	111	OMEX	667 049	8 903 590	7 550 585	1.002		
	h66x	92	I610Q, I660Q	412 542	8 751 528	7 606 230	1.018		
	auom	85	I660Q	620 326	9 525 561	7 722 840	1.003		
	euo2	58	OMEX	620 423	9 340 134	7 722 840	0.994		
	dub1	51	A6.0	660 474	8 738 458	7 223 862	1.007		
	Summary	**12 977**				**7 576 712**	**1.024**	**7 586 624**	**0.97**
Replication	**ukwa1**	1156	PsychChip		7 418 616	7 180 534	1.001		
	dutch	468	OMEX	302801	8 805 961	7 595 979	0.996		
	jst5	186	II1M		8 865 653	7 679 241	0.990		
	colo	176	GSA	460009	10 560 312	8 366 944	1.012		
	bmrom	126	OMEX	536719	8 957 237	7 543 990	1.005		
	bdtrs	125	PsychChip	298475	8 800 147	7 485 102	0.999		
	Summary	**2237**				**7 286 335**	**1.011**		

GWAS, genome-wide association study; λ, median genomic inflation factor.

Supplementary Table S3. Overview of the genome-wide association studies (GWASs) used as training data for single-nucleotide variant weights in the calculation of polygenic scores

Phenotype	Publication	Sample size (cases / controls)
Age at onset of bipolar disorder (leave-one-out)	Present study	12 977 / 0
Attention deficit hyperactivity disorder	Demontis et al. 2019 (15)	20 183 / 35 191
Autism spectrum disorder	Grove et al. 2019 (16)	18 381/ 27 969
Bipolar disorder (leave-one-out)	Stahl et al. 2019 (1)	20 352 / 31 358
Educational attainment	Lee et al. 2018 (17)	766 345 / 0
Major depressive disorder	Howard et al. 2019 (18)	170 756 / 329 443
Polarity at onset of bipolar disorder (leave-one-out)	Present Study	6 773
Schizophrenia	Pardinas et al. 2018 (19)	40 675 / 64 643

Supplementary Table S4. Analysis of disease characteristics in the combined analysis of German studies (PsyCourse and FOR2107 cohorts)

Independent variables:

1. Age at onset (AAO); after rank-based inverse-normal transformation
2. Polarity at onset (PAO) including mixed episodes (PAO, including mixed):
   0: Manic/hypomanic onset or a first manic/hypomanic and depressive episode within the same year
   1: Depressive onset
3. PAO excluding mixed episodes (PAO, excluding mixed)
   0: Manic/hypomanic onset
   1: Depressive onset
   Individuals with a first manic/hypomanic and depressive episode within the same year were excluded

Covariate: sex

Dichotomized dependent variables analyzed by logistic regression:

Delusions, hallucinations, current smoking, suicidal ideation, suicide attempts, education, and living together.

Here, an odds ratio (OR) >1 indicates that a higher AAO or a depressive onset was associated with a greater likelihood of having a positive score in the tested variable.

Continuous dependent outcome variables variables analyzed by linear regression:

Number of manic episodes per illness year and number of depressive episodes per illness year.

Here, a beta >0 indicates that a higher AAO or a depressive onset was associated with more manic or depressive episodes per illness year.

Variable	AAO					PAO, including mixed					PAO, excluding mixed				
	N	**OR**	**95% CI**	***P* value**	**Adj. *P* value**	**N**	**OR**	**95% CI**	***P* value**	**Adj. *P* value**	**N**	**OR**	**95% CI**	***P* value**	**Adj. *P* value**
Delusions	328	0.85	0.68-1.07	$1.67x10^{-1}$	$8.35x10^{-1}$	293	0.62	0.38-1.01	$5.48x10^{-2}$	$3.29x10^{-1}$	225	0.74	0.39-1.39	$3.45x10^{-1}$	$1.00x10^{0}$
Hallucinations	336	0.80	0.62-1.02	$7.49x10^{-2}$	$5.24x10^{-1}$	301	0.97	0.57-1.65	$9.21x10^{-1}$	$1.00x10^{0}$	232	1.25	0.60-2.58	$5.52x10^{-1}$	$1.00x10^{0}$
Current smoking	337	0.97	0.78-1.20	$7.72x10^{-1}$	$1.00x10^{0}$	302	0.84	0.53-1.33	$4.49x10^{-1}$	$1.00x10^{0}$	232	0.62	0.33-1.14	$1.24x10^{-1}$	$6.20x10^{-1}$
Suicidal ideation	334	0.58	0.44-0.77	$1.75x10^{-4}$	***1.58x10*$^{-3}$**	299	1.52	0.85-2.71	$1.59x10^{-1}$	$7.95x10^{-1}$	229	1.24	0.57-2.68	$5.92x10^{-1}$	$1.00x10^{0}$
Suicide attempt	273	0.77	0.60-1.00	$5.14x10^{-2}$	$4.11x10^{-1}$	256	1.80	1.06-3.05	$2.94x10^{-2}$	$2.06x10^{-1}$	186	2.37	1.11-5.05	$2.50x10^{-2}$	$1.50x10^{-1}$
Education	328	0.99	0.76-1.28	$9.12x10^{-1}$	$1.00x10^{0}$	294	1.31	0.76-2.24	$3.29x10^{-1}$	$1.00x10^{0}$	227	1.43	0.70-2.95	$3.27x10^{-1}$	$1.00x10^{0}$
Living together	48	1.28	0.70-2.34	$4.20x10^{-1}$	$1.00x10^{0}$	37	-	-	-		37	-	-	-	
	N	**B**	**SE**	***P* value**	**Adj. *P* value**	**N**	**B**	**SE**	***P* value**	**Adj. *P* value**	**N**	**B**	**SE**	***P* value**	**Adj. *P*-value**
Number of manic episodes per year of illness	267	0.10	0.06	$9.78x10^{-2}$	$5.87x10^{-1}$	242	-0.79	0.12	$3.64x10^{-10}$	***2.91x10*$^{-9}$**	187	-0.51	0.16	$1.55x10^{-3}$	**$1.085x10^{-2}$**
Number of depressive episodes per year of illness	252	0.08	0.06	$1.94x10^{-1}$	$8.35x10^{-1}$	245	0.05	0.13	$7.19x10^{-1}$	$1.00x10^{0}$	189	0.52	0.16	$1.03x10^{-3}$	**$8.24x10^{-3}$**

The number of manic/depressive episodes was divided by (years of illness)+1. For secondary analyses of the number of episodes not corrected for the years of illness, see the Supplementary Note 2.

OR, odds ratio; B, unstandardized beta; *P* value, unadjusted *P* value; Adj. *P* value, Bonferroni Holm corrected *P* value; N, total number of cases in model. Significant adjusted *P* values are indicated in bold.

Supplementary Table S5. Analysis of disease characteristics in Dutch BP sample (ucl2 and Dutch cohorts)

For a detailed description of the analyses, see Table S4.

Variable	AAO					PAO, including mixed					PAO, excluding mixed				
	N	OR	95% CI	*P* value	Adj. *P* value	N	OR	95% CI	*P* value	Adj. *P* value	N	OR	95% CI	*P* value	Adj. *P* value
Delusions	1284	0.67	0.59-0.76	$8.66x10^{-10}$	**$7.79x10^{-9}$**	1005	0.62	0.48-0.82	$7.43x10^{-4}$	**$5.20x10^{-3}$**	545	0.19	0.09-0.39	$5.01x10^{-6}$	**$4.51x10^{-5}$**
Hallucinations	1258	0.83	0.74-0.93	$1.83x10^{-3}$	**$7.32x10^{-3}$**	989	0.92	0.71-1.18	$5.08x10^{-1}$	$1.00x10^{0}$	541	0.70	0.45-1.09	$1.16x10^{-1}$	$3.48x10^{-1}$
Current smoking	1257	0.99	0.88-1.11	$8.38x10^{-1}$	$8.38x10^{-1}$	980	1.23	0.94-1.60	$1.24x10^{-1}$	$4.96x10^{-1}$	531	1.03	0.65-1.64	$9.01x10^{-1}$	$9.24x10^{-1}$
Suicidal ideation	1184	0.83	0.74-0.94	$2.59\ x10^{-3}$	**$7.77x10^{-3}$**	981	1.71	1.32-2.23	$5.56x10^{-5}$	**$4.45x10^{-4}$**	545	2.09	1.34-3.27	$1.17x10^{-3}$	**$8.19x10^{-3}$**
Suicide attempt	1264	0.78	0.68-0.89	$2.03x10^{-4}$	**$1.42x10^{-3}$**	1006	1.52	1.15-2.01	$2.94x10^{-3}$	**$1.76x10^{-2}$**	550	1.94	1.14-3.31	$1.427x10^{-2}$	$8.58x10^{-2}$
Education	1308	1.21	1.08-1.35	$9.51x10^{-4}$	**$4.76x10^{-3}$**	1025	1.02	0.79-1.30	$8.88x10^{-1}$	$1.00x10^{0}$	557	0.67	0.43-1.04	$7.23x10^{-2}$	$2.89x10^{-1}$
Living together	1309	1.28	1.15-1.44	$1.43x10^{-5}$	**$1.14x10^{-4}$**	1025	0.86	0.67-1.10	$2.28x10^{-1}$	$6.84x10^{-1}$	557	1.18	0.76-1.82	$4.62x10^{-1}$	$9.24x10^{-1}$
	N	**B**	**SE**	***P* value**	**Adj. *P* value**	**N**	**B**	**SE**	***P* value**	**Adj. *P* value**	**N**	**B**	**SE**	***P* value**	**Adj. *P* value**
Number of manic episodes per year of illness	1171	0.11	0.03	$3.17x10^{-4}$	**$1.90x10^{-3}$**	916	-0.31	0.07	$3.54x10^{-6}$	**$3.19x10^{-5}$**	498	-0.25	0.12	$3.03x10^{-2}$	$1.52x10^{-1}$
Number of depressive episodes per year of illness	981	0.06	0.03	$5.04x10^{-2}$	$1.01x10^{-1}$	808	0.14	0.07	$3.91x10^{-2}$	$1.96x10^{-1}$	445	0.35	0.11	$1.01x10^{-3}$	**$8.08x10^{-3}$**

The number of manic/depressive episodes was divided by (years of illness)+1. For secondary analyses of the number of episodes not corrected for the years of illness, see the Supplementary Note 2.

OR, odds ratio; B, unstandardized beta; *P* value, unadjusted *P* value; Adj. *P* value, Bonferroni Holm corrected *P* value; N, total number of cases in model. Significant adjusted *P* values are indicated in bold.

Supplementary Table S6: Differences in age at onset (AAO) between subgroups

Non-parametric pairwise Mann-Whitney U tests (median, χ^2 statistic (chi^2), *P* value) and linear regression model (beta, SE, *P* value) on the untransformed age at onset.
For these analyses, the default definition of AAO was the diagnostic interview; the default continent, Europe; the default subtype, BD-I; and the default sex, male.
Separate Mann-Whitney U tests were used to assess continent, definition, subtype, and sex. A single, multivariable model containing all listed variables was used for the linear regression. Thus, the coefficients from the linear regression model are corrected for the other variables displayed, while the Mann-Whitney U test results are univariate.

	Mann-Whitney U tests			Linear regression		
Variable	**Median**	**Chi^2**	***P* value**	**Beta**	**SE**	***P* value**
Continent: Europe	24					
Continent: North America	18	1202.3	**1.97E-263**	-4.70	0.22	**5.12E-96**
Continent: Australia	19.5	47.69	**4.97E-12**	-2.18	0.58	**1.54E-04**
Definition: Diagnostic interview	19					
Definition: Impairment/help-seeking	23	517.64	**1.38E-114**	1.44	0.22	**1.32E-10**
Definition: Pharmacotherapy	30	490.29	**1.23E-108**	6.73	0.45	**3.40E-50**
Definition: Mixed	23	143.95	**3.63E-33**	-1.85	1.39	1.84E-01
Subtype: BD-I	21					
Subtype: BD-II	22	17.13	**3.48E-05**	0.86	0.28	**2.43E-03**
Subtype: BD-NOS	20	0.04	0.835	0.97	1.05	3.55E-01
Sex: Male	22					
Sex: Female	21	23.79	**1.07E-06**	-0.86	0.18	**1.11E-06**

BD-NOS, bipolar disorder not otherwise specified

Supplementary Table S7: Genome-wide association study on age at onset (AAO) in bipolar disorder

Genome-wide significant locus at rs1610275 on chromosome 16 for AAO in the primary and replication analyses.

	Allele Frequency	INFO Score	Beta	SE	*P*	N
Discovery	0.319 (G)	0.969	0.075	0.0135	3.388E-08	12977
Replication	0.321 (G)	0.982	-0.042	0.0329	0.1929	2237

Supplementary Table S8: Results of PGS analyses

Please see the separate Excel file.
Significance levels: Bonferroni, significant after correction for 96 tests, $P < 5.2\times10^{-4}$; Nominal, $P < 0.05$; n.s., not significant. *P* 1-sided: one-sided *P* value, based on the hypothesis that all polygenic scores (PGSs) except the PGS for age at onset (AAO) show a negative association with AAO. R^2 complete: R^2 complete model; R^2 null: R^2 null model (without PGS); R^2 PGS: R^2 explained by the PGS; N. R^2: Nagelkerke's pseudo-R^2. N: sample size; I^2/Q: Measures of meta-analysis heterogeneity.

Supplementary Table S9. Overview of characteristics for phenotypic analyses

Variable/*Cohort*	Instrument	Items	Outcome
Delusions			Delusions lifetime (dichotomous); 0 = No, has never experienced any of the delusions assessed with the instrument 1 = Yes, has experienced at least one of the delusions that were assessed
PsyCourse	SCID-I (20)	Delusion of reference, Persecutory delusion, Delusions of grandiosity, Somatic delusion, Other delusion, Delusion of control, Thought withdrawal, Religious delusion, Delusion of guilt, Delusion of jealousy, Erotomanic delusion, Cotard delusion, Delusion of poverty*	
FOR2107	SCID-I	Delusion of reference, Persecutory delusion, Delusions of grandiosity, Somatic delusion, Other delusion, Ego disturbance, Thought broadcast*	
Dutch BP	SCID-I	Delusion of reference, Persecutory delusion, Delusion of grandiosity, Somatic delusion, Other delusion, Religious delusion, Delusion of guilt or sin, Delusion of jealousy, Erotomanic delusion, Delusion of being controlled Thought insertion, Thought withdrawal, Thought broadcasting, Bizarre delusion*	
Hallucinations			Lifetime hallucinations (dichotomous); 0 = No, has never experienced any of the hallucinations assessed with the instrument 1 = Yes, has experienced at least one of the hallucinations that were assessed
PsyCourse	SCID-I	Auditory hallucinations, Visual hallucinations, Olfactory hallucinations, Gustatory hallucinations, Tactile hallucinations*	
FOR2107	SCID-I	Auditory hallucinations, Visual hallucinations, Tactile hallucinations, Other hallucinations*	
Dutch BP	SCID-I	Auditory hallucinations, Visual hallucinations, Tactile hallucinations, Other hallucinations*	
Current smoking			Current smoking (dichotomous); 0 = No 1 = Yes
PsyCourse	Structured interview	One item: Have you ever smoked cigarettes, cigars, pipe, or other tobacco products? [Never smoked (or < 100 cigarettes during lifetime); Yes, current smoker; Former smoker (quit smoking more than 3 months ago)]	
FOR2107	Fagerström (self-report) (21)	One item: Current smoker? [No, Yes, Missing]	

Dutch BP	Fagerström (self-report) (21)	One item: Do you smoke currently? [No, Yes, Missing]	
Suicidal ideation			Suicidal ideation; (dichotomous) 0 = No 1 = Yes
PsyCourse	SCID-I	Suicidal ideation, lifetime	
FOR2107	OPCRIT	Suicidal ideation, lifetime	
Dutch BP	SCID-I	Suicidal ideation during depressive episode	
Suicide attempt			Lifetime suicide attempt; (dichotomous) 0 = No 1 = Yes
PsyCourse	SCID-I	Suicide attempt, lifetime [No = 1; interrupted attempt = 2; Yes = 3]	
FOR2107	NA	NA	
Dutch BP	Combination of items SCID-I and Comprehensive Assessment of Symptoms and History (CASH) (22)	SCID-I: suicide attempt during depressive episode CASH: Suicide attempt, lifetime	
Education			Educational attainment, (dichotomous); 0=Lower educational attainment (PsyCourse: 0, 1, 2, 3, 4, 5; FOR: 1, 2, 3, 4, 5, 6, 7, 8; Dutch BP: 1, 2, 3, 4) 1= Higher educational attainment (PsyCourse: 6; FOR: 9, 10, Dutch BP: 5, 6)
PsyCourse	Interview	*Education (ordinal [0,1,2,3,4,5,6], v1_ed_status):* This scale was newly created by merging the original items**. High school-level education (categorical); NA = no information/missing 0 = no graduation 1 = high school completed after grade 9 2 = high school completed after grade 10 OR polytechnic high school 3 = technical high school OR European general higher education entrance qualification 999 = still in school/other type of school diploma Professional education (categorical); NA=missing or no information	

		0=no professional education/vocational training in a company but no apprenticeship/ vocational training program/in professional education 1= apprenticeship 2=vocational training in a company /vocational and school-based training 3= degree from a university or university of applied sciences 999=other professional degree More than 1 answer was possible, because people may have several professional degrees.	
FOR2107	Interview	Highest completed educational level 1 = No school diploma 2 = elementary school 3 = diploma from high school completed after grade 9 4 = high school completed after grade 10 5 = technical diploma 6 = high school diploma 7 = apprenticeship 8 = master craftsman 9 = Bachelors 10 = Masters	
Dutch BP	Self-report questionnaire	Highest completed educational level 1 = Low education 2 = intermediate secondary education 3 = intermediate professional education 4 = high preparatory vocational/pre-university 5 = Bachelor 6 = Master or PhD degree	
Living together			Living together, (dichotomous); 0=Not living together with a partner (living alone, living with parents/relatives divorced, divorced from bed and board, never married) 1=living together with a partner or widowed (living with a partner, living with husband/wife, married or living together, widowed)
PsyCourse	NA	NA	
FOR2107	SCID-I	Current living situation 1 = Living alone 2 = Living with partner 3 = Living with husband/wife 4 = Living with parents/relatives 5 = Living in a community	

		6 = Living in a treatment facility = 6 7 = other 5, 6, and 7 are recoded as missing because in these cases it is unclear whether someone is living with a partner	
Dutch BP	SCID-I	Current marital status 1 = Married or living together 2 = Widowed 3 = Divorced 4 = Divorce from bed and board 5 = Never married	
Number of manic episodes			Rank-normalized number of episodes; continuous number of episodes/(years of illness + 1)
PsyCourse	SCID-I	Total number of manic episodes	
FOR2107	SCID-I	Total number of manic episodes	
Dutch BP	SCID-I	Total number of manic episodes	
Number of depressive episodes			Rank-normalized number of episodes; continuous number of episodes/(years of illness + 1)
PsyCourse	SCID-I	Total number of depressive episodes	
FOR2107	SCID-I	Total number of depressive episodes	
Dutch BP	SCID-I	Total number of depressive episodes	

SCID-I, Structured Clinical Interview for DSM-IV; CASH, Comprehensive Assessment of Symptoms and History

*Questionable is coded as absent. However, if screener questions are coded questionable, but specifier items are coded as present, then Delusions lifetime and Hallucinations lifetime are coded as present.

** School and university/professional education were assessed separately in the interview. To combine school and university/ professional education, we transformed both scales to values that could be added together to form an “educational attainment” variable. High school-level education was transformed into an ordinal scale from 0 to 3 (people still in high school at the time of the interview were assigned “NA”). University/professional education was also transformed into an ordinal scale from 0 to 3. These 2 scales were added together to give an ordinal educational status scale, which ranged from 0 to 6.

Authors of the Bipolar Disorder Working Group of the Psychiatric Genomics Consortium

Eli A Stahl 1,2,3†
Gerome Breen 4,5†
Andreas J Forstner 6,7,8,9,10†
Andrew McQuillin 11†
Stephan Ripke 12,13,14†
Vassily Trubetskoy 13
Manuel Mattheisen 15,16,17,18,19
Yunpeng Wang 20,21
Jonathan R I Coleman 4,5
Héléna A Gaspar 4,5
Christiaan A de Leeuw 22
Stacy Steinberg 23
Jennifer M Whitehead Pavlides 24
Maciej Trzaskowski 25
Tune H Pers 3,26
Peter A Holmans 27
Liam Abbott 12
Esben Agerbo 19,28,29
Huda Akil 30
Diego Albani 31
Ney Alliey-Rodriguez 32
Thomas D Als 15,16,19
Adebayo Anjorin 33
Verneri Antilla 14
Swapnil Awasthi 13
Judith A Badner 34
Marie Bækvad-Hansen 19,35
Jack D Barchas 36
Nicholas Bass 11
Michael Bauer 37
Richard Belliveau 12
Sarah E Bergen 38
Carsten Bøcker Pedersen 19,28,29
Erlend Bøen 39
Marco Boks 40
James Boocock 41
Monika Budde 42
William Bunney 43
Margit Burmeister 44
Jonas Bybjerg-Grauholm 19,35
William Byerley 45
Miquel Casas 46,47,48,49
Felecia Cerrato 12
Pablo Cervantes 50
Kimberly Chambert 12
Alexander W Charney 2
Danfeng Chen 12
Claire Churchhouse 12,14
Toni-Kim Clarke 51
William Coryell 52
David W Craig 53
Cristiana Cruceanu 50,54
Piotr M Czerski 55
Anders M Dale 56,57,58,59
Simone de Jong 4,5
Franziska Degenhardt 8,9
Jurgen Del-Favero 60
J Raymond DePaulo 61
Srdjan Djurovic 62,63
Amanda L Dobbyn 1,2
Ashley Dumont 12
Torbjørn Elvsåshagen 64,65
Valentina Escott-Price 27
Chun Chieh Fan 59
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Matthew Flickinger 66
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Elaine K Green 77
Melissa J Green 78
Tiffany A Greenwood 58
Jakob Grove 15,16,19,79
Weihua Guan 80
José Guzman Parra 81
Marian L Hamshere 27
Martin Hautzinger 82
Urs Heilbronner 42
Stefan Herms 6,8,9,10

† Equal contribution, * Co-last authors
^ deceased.

1. Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, US
2. Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, US
3. Medical and Population Genetics, Broad Institute, Cambridge, MA, US
4. MRC Social, Genetic and Developmental Psychiatry Centre, King's College London, London, GB
5. NIHR BRC for Mental Health, King's College London, London, GB
6. Human Genomics Research Group, Department of Biomedicine, University of Basel, Basel, CH
7. Department of Psychiatry (UPK), University of Basel, Basel, CH
8. Institute of Human Genetics, University of Bonn, School of Medicine & University Hospital Bonn, Bonn, DE
9. Department of Genomics, Life&Brain Center, University of Bonn, Bonn, DE
10. Institute of Medical Genetics and Pathology, University Hospital Basel, Basel, CH
11. Division of Psychiatry, University College London, London, GB
12. Stanley Center for Psychiatric Research, Broad Institute, Cambridge, MA, US
13. Department of Psychiatry and Psychotherapy, Charité - Universitätsmedizin, Berlin, DE
14. Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, MA, US
15. iSEQ, Center for Integrative Sequencing, Aarhus University, Aarhus, DK
16. Department of Biomedicine - Human Genetics, Aarhus University, Aarhus, DK
17. Department of Clinical Neuroscience, Centre for Psychiatry Research, Karolinska Institutet, Stockholm, SE
18. Department of Psychiatry, Psychosomatics and Psychotherapy, Center of Mental Health, University Hospital Würzburg, Würzburg, DE
19. iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, DK
20. Institute of Biological Psychiatry, Mental Health Centre Sct. Hans, Copenhagen, DK
21. Institute of Clinical Medicine, University of Oslo, Oslo, NO
22. Department of Complex Trait Genetics, Center for Neurogenomics and Cognitive Research, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam, NL
23. deCODE Genetics / Amgen, Reykjavik, IS
24. Queensland Brain Institute, The University of Queensland, Brisbane, QLD, AU
25. Institute for Molecular Bioscience, The University of Queensland, Brisbane, QLD, AU
26. Division of Endocrinology and Center for Basic and Translational Obesity Research, Boston Children's Hospital, Boston, MA, US
27. Medical Research Council Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, Cardiff, GB
28. National Centre for Register-Based Research, Aarhus University, Aarhus, DK
29. Centre for Integrated Register-based Research, Aarhus University, Aarhus, DK
30. Molecular & Behavioral Neuroscience Institute, University of Michigan, Ann Arbor, MI, US
31. NEUROSCIENCE, Istituto Di Ricerche Farmacologiche Mario Negri, Milano, IT
32. Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, IL, US
33. Psychiatry, Berkshire Healthcare NHS Foundation Trust, Bracknell, GB
34. Psychiatry, Rush University Medical Center, Chicago, IL, US

35. Center for Neonatal Screening, Department for Congenital Disorders, Statens Serum Institut, Copenhagen, DK
36. Department of Psychiatry, Weill Cornell Medical College, New York, NY, US
37. Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, DE
38. Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, SE
39. Department of Psychiatric Research, Diakonhjemmet Hospital, Oslo, NO
40. Psychiatry, UMC Utrecht Hersencentrum Rudolf Magnus, Utrecht, NL
41. Human Genetics, University of California Los Angeles, Los Angeles, CA, US
42. Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Munich, DE
43. Department of Psychiatry and Human Behavior, University of California, Irvine, Irvine, CA, US
44. Molecular & Behavioral Neuroscience Institute and Department of Computational Medicine & Bioinformatics, University of Michigan, Ann Arbor, MI, US
45. Psychiatry, University of California San Francisco, San Francisco, CA, US
46. Instituto de Salud Carlos III, Biomedical Network Research Centre on Mental Health (CIBERSAM), Madrid, ES
47. Department of Psychiatry, Hospital Universitari Vall d´Hebron, Barcelona, ES
48. Department of Psychiatry and Forensic Medicine, Universitat Autònoma de Barcelona, Barcelona, ES
49. Psychiatric Genetics Unit, Group of Psychiatry Mental Health and Addictions, Vall d´Hebron Research Institut (VHIR), Universitat Autònoma de Barcelona, Barcelona, ES
50. Department of Psychiatry, Mood Disorders Program, McGill University Health Center, Montreal, QC, CA
51. Division of Psychiatry, University of Edinburgh, Edinburgh, GB
52. University of Iowa Hospitals and Clinics, Iowa City, IA, US
53. Translational Genomics, USC, Phoenix, AZ, US
54. Department of Translational Research in Psychiatry, Max Planck Institute of Psychiatry, Munich, DE
55. Department of Psychiatry, Laboratory of Psychiatric Genetics, Poznan University of Medical Sciences, Poznan, PL
56. Department of Neurosciences, University of California San Diego, La Jolla, CA, US
57. Department of Radiology, University of California San Diego, La Jolla, CA, US
58. Department of Psychiatry, University of California San Diego, La Jolla, CA, US
59. Department of Cognitive Science, University of California San Diego, La Jolla, CA, US
60. Applied Molecular Genomics Unit, VIB Department of Molecular Genetics, University of Antwerp, Antwerp, Belgium
61. Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, US
62. Department of Medical Genetics, Oslo University Hospital Ullevål, Oslo, NO
63. NORMENT, KG Jebsen Centre for Psychosis Research, Department of Clinical Science, University of Bergen, Bergen, NO
64. Department of Neurology, Oslo University Hospital, Oslo, NO
65. NORMENT, KG Jebsen Centre for Psychosis Research, Oslo University Hospital, Oslo, NO

66. Center for Statistical Genetics and Department of Biostatistics, University of Michigan, Ann Arbor, MI, US
67. Department of Medical & Molecular Genetics, Indiana University, Indianapolis, IN, US
68. Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, DE
69. Center for Neurobehavioral Genetics, University of California Los Angeles, Los Angeles, CA, US
70. Department of Molecular Medicine and Surgery, Karolinska Institutet and Center for Molecular Medicine, Karolinska University Hospital, Stockholm, SE
71. Department of Clinical Neuroscience, Karolinska Institutet and Center for Molecular Medicine, Karolinska University Hospital, Stockholm, SE
72. Child and Adolescent Psychiatry Research Center, Stockholm, SE
73. Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Göttingen, DE
74. Department of Psychiatry, Dalhousie University, Halifax, NS, CA
75. Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, QLD, AU
76. Department of Psychological Medicine, University of Worcester, Worcester, GB
77. School of Biomedical and Healthcare Sciences, Plymouth University Peninsula Schools of Medicine and Dentistry, Plymouth, GB
78. School of Psychiatry, University of New South Wales, Sydney, NSW, AU
79. Bioinformatics Research Centre, Aarhus University, Aarhus, DK
80. Biostatistics, University of Minnesota System, Minneapolis, MN, US
81. Mental Health Department, University Regional Hospital, Biomedicine Institute (IBIMA), Málaga, ES
82. Department of Psychology, Eberhard Karls Universität Tübingen, Tubingen, DE
83. Department of Psychiatry and Behavioral Sciences, Howard University Hospital, Washington, DC, US
84. Center for Multimodal Imaging and Genetics, University of California San Diego, La Jolla, CA, US
85. Psychiatrie Translationnelle, Inserm U955, Créteil, FR
86. Faculté de Médecine, Université Paris Est, Créteil, FR
87. Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, ON, CA
88. Neurogenetics Section, Centre for Addiction and Mental Health, Toronto, ON, CA
89. Department of Psychiatry, University of Toronto, Toronto, ON, CA
90. Institute of Medical Sciences, University of Toronto, Toronto, ON, CA
91. Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt, Frankfurt am Main, DE
92. Cell Biology, SUNY Downstate Medical Center College of Medicine, Brooklyn, NY, US
93. Institute for Genomic Health, SUNY Downstate Medical Center College of Medicine, Brooklyn, NY, US
94. ISGlobal, Barcelona, ES
95. Psychiatry, Altrecht, Utrecht, NL
96. Psychiatry, GGZ inGeest, Amsterdam, NL
97. Psychiatry, VU medisch centrum, Amsterdam, NL
98. Psychiatry, North East London NHS Foundation Trust, Ilford, GB
99. Clinic for Psychiatry and Psychotherapy, University Hospital Cologne, Cologne, DE

100. Psychiatric and Neurodevelopmental Genetics Unit, Massachusetts General Hospital, Boston, MA, US
101. HudsonAlpha Institute for Biotechnology, Huntsville, AL, US
102. Department of Human Genetics, University of Michigan, Ann Arbor, MI, US
103. Psychiatry, University of Illinois at Chicago College of Medicine, Chicago, IL, US
104. Max Planck Institute of Psychiatry, Munich, DE
105. Mental Health, NHS 24, Glasgow, GB
106. Division of Psychiatry, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, GB
107. Psychiatry, Brigham and Women's Hospital, Boston, MA, US
108. Department of Psychiatry and Psychotherapy, University of Bonn, Bonn, DE
109. Department of Genetics, Harvard Medical School, Boston, MA, US
110. Department of Psychiatry, University of Michigan, Ann Arbor, MI, US
111. Genetic Cancer Susceptibility Group, International Agency for Research on Cancer, Lyon, FR
112. Estonian Genome Center, University of Tartu, Tartu, EE
113. Discipline of Biochemistry, Neuroimaging and Cognitive Genomics (NICOG) Centre, National University of Ireland, Galway, Galway, IE
114. Neuropsychiatric Genetics Research Group, Dept of Psychiatry and Trinity Translational Medicine Institute, Trinity College Dublin, Dublin, IE
115. Institute of Neuroscience and Medicine (INM-1), Research Centre Jülich, Jülich, DE
116. Research/Psychiatry, Veterans Affairs San Diego Healthcare System, San Diego, CA, US
117. Department of Clinical Sciences, Psychiatry, Umeå University Medical Faculty, Umeå, SE
118. Department of Clinical Psychiatry, Psychiatry Clinic, Clinical Center University of Sarajevo, Sarajevo, BA
119. Department of Neurobiology, Care sciences, and Society, Karolinska Institutet and Center for Molecular Medicine, Karolinska University Hospital, Stockholm, SE
120. Psychiatry, Harvard Medical School, Boston, MA, US
121. Division of Clinical Research, Massachusetts General Hospital, Boston, MA, US
122. Outpatient Clinic for Bipolar Disorder, Altrecht, Utrecht, NL
123. Department of Psychiatry, Washington University in Saint Louis, Saint Louis, MO, US
124. Department of Biochemistry and Molecular Biology II, Institute of Neurosciences, Center for Biomedical Research, University of Granada, Granada, ES
125. Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY, US
126. Medicine, Psychiatry, Biomedical Informatics, Vanderbilt University Medical Center, Nashville, TN, US
127. Department of Health Sciences Research, Mayo Clinic, Rochester, MN, US
128. Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, US
129. Rush University Medical Center, Chicago, IL, US
130. Scripps Translational Science Institute, La Jolla, CA, US
131. Neuroscience Research Australia, Sydney, NSW, AU
132. Faculty of Medicine, Department of Psychiatry, School of Health Sciences, University of Iceland, Reykjavik, IS
133. Div Mental Health and Addiction, Oslo University Hospital, Oslo, NO
134. NORMENT, University of Oslo, Oslo, NO

135. Psychiatry and the Behavioral Sciences, University of Southern California, Los Angeles, CA, US
136. Mood Disorders, PsyQ, Rotterdam, NL
137. Institute for Medical Sciences, University of Aberdeen, Aberdeen, UK
138. Research Division, Federal Institute for Drugs and Medical Devices (BfArM), Bonn, DE
139. Centre for Addiction and Mental Health, Toronto, ON, CA
140. Neurogenomics, TGen, Los Angeles, AZ, US
141. Psychiatry, Psychiatrisches Zentrum Nordbaden, Wiesloch, DE
142. Computational Sciences Center of Emphasis, Pfizer Global Research and Development, Cambridge, MA, US
143. Department of Biostatistics, Princess Margaret Cancer Centre, Toronto, ON, CA
144. Dalla Lana School of Public Health, University of Toronto, Toronto, ON, CA
145. Psychological Medicine, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, GB
146. Department of Mental Health, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, US
147. Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, US
148. NORMENT, KG Jebsen Centre for Psychosis Research, Division of Mental Health and Addiction, Institute of Clinical Medicine and Diakonhjemmet Hospital, University of Oslo, Oslo, NO
149. National Institute of Mental Health, Klecany, CZ
150. Discipline of Psychiatry, University of Adelaide, Adelaide, SA, AU
151. Department of Psychiatry and Addiction Medicine, Assistance Publique - Hôpitaux de Paris, Paris, FR
152. Paris Bipolar and TRD Expert Centres, FondaMental Foundation, Paris, FR
153. UMR-S1144 Team 1: Biomarkers of relapse and therapeutic response in addiction and mood disorders, INSERM, Paris, FR
154. Psychiatry, Université Paris Diderot, Paris, FR
155. Psychiatry, University of Pennsylvania, Philadelphia, PA, US
156. Department of Psychiatry, University of Münster, Münster, DE
157. Division of Endocrinology, Children's Hospital Boston, Boston, MA, US
158. Centre for Affective Disorders, Institute of Psychiatry, Psychology and Neuroscience, London, GB
159. Department of Psychiatry & Psychology, Mayo Clinic, Rochester, MN, US
160. School of Medical Sciences, University of New South Wales, Sydney, NSW, AU
161. Department of Human Genetics, University of Chicago, Chicago, IL, US
162. Biometric Psychiatric Genetics Research Unit, Alexandru Obregia Clinical Psychiatric Hospital, Bucharest, RO
163. Institute of Neuroscience and Physiology, University of Gothenburg, Gothenburg, SE
164. INSERM, Paris, FR
165. Department of Medical & Molecular Genetics, King's College London, London, GB
166. Neuroscience Therapeutic Area, Janssen Research and Development, LLC, Titusville, NJ, US
167. Cancer Epidemiology and Prevention, M. Sklodowska-Curie Cancer Center and Institute of Oncology, Warsaw, PL
168. School of Psychology, The University of Queensland, Brisbane, QLD, AU
169. Research Institute, Lindner Center of HOPE, Mason, OH, US

170. Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, GB
171. Human Genetics Branch, Intramural Research Program, National Institute of Mental Health, Bethesda, MD, US
172. Division of Mental Health and Addiction, Oslo University Hospital, Oslo, NO
173. Division of Mental Health and Addiction, University of Oslo, Institute of Clinical Medicine, Oslo, NO
174. Institute of Molecular and Cell Biology, University of Tartu, Tartu, EE
175. Mental Health, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology - NTNU, Trondheim, NO
176. Psychiatry, St Olavs University Hospital, Trondheim, NO
177. Psychosis Research Unit, Aarhus University Hospital, Risskov, DK
178. Munich Cluster for Systems Neurology (SyNergy), Munich, DE
179. University of Liverpool, Liverpool, GB
180. Psychiatry and Human Genetics, University of Pittsburgh, Pittsburgh, PA, US
181. Mental Health Services in the Capital Region of Denmark, Mental Health Center Copenhagen, University of Copenhagen, Copenhagen, DK
182. Division of Psychiatry, Haukeland Universitetssjukehus, Bergen, NO
183. Faculty of Medicine and Dentistry, University of Bergen, Bergen, NO
184. Human Genetics and Computational Biomedicine, Pfizer Global Research and Development, Groton, CT, US
185. College of Medicine Institute for Genomic Health, SUNY Downstate Medical Center College of Medicine, Brooklyn, NY, US
186. Department of Clinical Genetics, Amsterdam Neuroscience, Vrije Universiteit Medical Center, Amsterdam, NL
187. Department of Neurology and Neurosurgery, McGill University, Faculty of Medicine, Montreal, QC, CA
188. Montreal Neurological Institute and Hospital, Montreal, QC, CA
189. Department of Biomedical and NeuroMotor Sciences, University of Bologna, Bologna, IT
190. Department of Psychiatry, Massachusetts General Hospital, Boston, MA, US
191. Psychiatric and Neurodevelopmental Genetics Unit (PNGU), Massachusetts General Hospital, Boston, MA, US
192. Faculty of Medicine, University of Iceland, Reykjavik, IS
193. Department of Psychiatry, Hospital Namsos, Namsos, NO
194. Department of Neuroscience, Norges Teknisk Naturvitenskapelige Universitet Fakultet for naturvitenskap og teknologi, Trondheim, NO
195. Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC, US
196. Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, US
197. Department of Psychiatry, McGill University, Montreal, QC, CA
198. Dept of Psychiatry, Sankt Olavs Hospital Universitetssykehuset i Trondheim, Trondheim, NO
199. Clinical Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, ES
200. Institute of Biological Psychiatry, MHC Sct. Hans, Mental Health Services Copenhagen, Roskilde, DK
201. Department of Clinical Medicine, University of Copenhagen, Copenhagen, DK
202. Psychiatry, Indiana University School of Medicine, Indianapolis, IN, US

203. Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, IN, US

Authors of the Colombia-US Cross Disorder Collaboration in Psychiatric Genetics Consortium

Susan K. Service 1 MSc,
Cristian Vargas Upegui 2 MD,
Mauricio Castaño Ramírez 3 MD,
Luis Guillermo Agudelo Arango 2 MD,
Ana M. Díaz-Zuluaga 1 MD,
Juanita Melo Espejo 2 MD,
Juan David Palacio 2 MD,
Sergio Ruiz Sánchez 2 BS,
Johanna Valencia 2 BS,
Terri M. Teshiba 1 BA,
Benjamin B. Brodey 4 MD,
Loes Olde Loohuis 1 PhD,
Ruben C. Gur 5 PhD,
Chiara Sabatti 6 PhD,
Javier I. Escobar 7 MD,
Victor I. Reus 8 MD,
Carrie E. Bearden 1 PhD,
Carlos Lopez Jaramillo 2 MD,
Nelson B. Freimer 1 MD.

1. Center for Neurobehavioral Genetics, Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles, Los Angeles, USA
2. Department of Psychiatry, University of Antioquía, Medellín, Colombia
3. Department of Mental Health and Human Behavior, University of Caldas, Manizales, Colombia
4. TeleSage, Inc., Chapel Hill, USA
5. Department of Psychiatry, University of Pennsylvania School of Medicine; Philadelphia, USA
6. Departments of Biomedical Data Science and Statistics, Stanford University, Stanford, USA
7. Department of Psychiatry, Rutgers Robert Wood Johnson Medical School, New Brunswick, USA
8. Department of Psychiatry, University of California San Francisco, San Francisco, USA

Authors of the International Consortium on Lithium Genetics

1.	Bernhard T.	Baune,	Discipline of Psychiatry,	University of Adelaide, Adelaide,	Australia
2.	Jan	Fullerton,	Mental Illness (Schofield Group),	Neuroscience Research Australia, Sydney,	Australia
3.	Philip B.	Mitchell,	School of Psychiatry,	University of New South Wales, and Black Dog Institute, Sydney,	Australia
4.	Peter R.	Schofield,	Mental Illness (Schofield Group),	Neuroscience Research Australia, Sydney,	Australia
5.	Naomi R.	Wray,	The University of Queensland, Queensland Brain Institute,	Brisbane, Queensland,	Australia
6.	Adam	Wright,	School of Psychiatry,	University of New South Wales, and Black Dog Institute, Sydney,	Australia
7.	Susanne A.	Bengesser,	Special outpatient center for bipolar affective disorder,	Medical University of Graz, Graz,	Austria
8.	Eva	Reininghaus,	Special outpatient center for bipolar affective disorder,	Medical University of Graz, Graz,	Austria

9.	Claudio E. M.	Banzato,	Department of Psychiatry,	University of Campinas (Unicamp), Campinas,	Brazil
10.	Clarissa	Dantas,	Department of Psychiatry,	University of Campinas (Unicamp), Campinas,	Brazil
11.	Martin	Alda,	Department of Psychiatry,	Dalhousie University, Halifax, Nova Scotia,	Canada
12.	Cristiana	Cruceanu,	Douglas Mental Health University Institute,	McGill University, Montreal,	Canada
13.	Julie	Garnham,	Department of Psychiatry,	Dalhousie University, Halifax, Nova Scotia,	Canada
14.	Paul	Grof,	Mood Disorders Center of Ottawa,		Canada
15.	Glenda	MacQueen,	Department of Psychiatry,	University of Calgary, Calgary,	Canada
16.	Guy	Rouleau,	Montreal Neurological Institute and Hospital,	McGill University, Montreal,	Canada
17.	Claire	Slaney,	Department of Psychiatry,	Dalhousie University, Halifax, Nova Scotia,	Canada
18.	Gustavo	Turecki,	Douglas Mental Health University Institute,	McGill University, Montreal,	Canada
19.	L. Trevor	Young,	Department of Psychiatry,	University of British Columbia, Vancouver,	Canada
20.	Carlos A.	López Jaramillo,	Department of Psychiatry,	University of Antioquia, Medellín, Medellín,	Colombia
21.	Tomás	Novák,	Prague Psychiatric Center and 3rd Faculty of Medicine,	Charles University, Prague,	Czech Republic
22.	Pavla	Stopkova,	Prague Psychiatric Center and 3rd Faculty of Medicine,	Charles University, Prague,	Czech Republic
23.	Frank	Bellivier,	INSERM UMR-S 1144 - Pôle de Psychiatrie,	AP-HP, Groupe Hospitalier Lariboisière-F. Widal, Paris,	France
24.	Clara	Brichant-Petitjean,	INSERM UMR-S 1144 - Pôle de Psychiatrie,	AP-HP, Groupe Hospitalier Lariboisière-F. Widal, Paris,	France
25.	Bruno	Etain,	Inserm U955, Psychiatrie Génétique,	Créteil,	France
26.	Bruno	Etain,	Université Paris Est, Faculté de Médecine,	Créteil,	France
27.	Bruno	Etain,	Fondation FondaMental,	Créteil,	France
28.	Bruno	Etain,	Assistance Publique-Hôpitaux de Paris,	Hôpital Albert Chenevier - Henri Mondor, Pôle de Psychiatrie, Créteil,	France
29.	Sébastien	Gard,	Service de psychiatrie,	Hôpital Charles Perrens, Bordeaux,	France
30.	Stéphane	Jamain,	Inserm U955, Psychiatrie Génétique,	Créteil,	France
31.	Stéphane	Jamain,	Université Paris Est, Faculté de Médecine,	Créteil,	France
32.	Stéphane	Jamain,	Fondation FondaMental,	Créteil,	France
33.	Jean-Pierre	Kahn,	Service de Psychiatrie et Psychologie Clinique,	Centre Hospitalier Universitaire de Nancy, Nancy,	France
34.	Jean-Pierre	Kahn,	Université de Lorraine,	Nancy,	France
35.	Marion	Leboyer,	Inserm U955, Psychiatrie Génétique,	Créteil,	France
36.	Marion	Leboyer,	Université Paris Est, Faculté de Médecine,	Créteil,	France
37.	Marion	Leboyer,	Fondation FondaMental,	Créteil,	France
38.	Marion	Leboyer,	Assistance Publique-Hôpitaux de Paris,	Hôpital Albert Chenevier - Henri Mondor, Pôle de Psychiatrie, Créteil,	France
39.	Mazda	Adli,	Department of Psychiatry and Psychotherapy, Charité - Universitätsmedizin Berlin,	Campus Charité Mitte & Fliedner Klinik Berlin,	Germany

40.	Mazda	Adli,	Fliedner Klinik Berlin,	Berlin,	Germany
41.	Michael	Bauer,	Department of Psychiatry and Psychotherapy,	University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden,	Germany
42.	Sven	Cichon,	Institute of Human Genetics, Department of Genomics, Life and Brain Center,	University of Bonn, Bonn,	Germany
43.	Sven	Cichon,	Institute of Neuroscience and Medicine (INM-1), Genomic Imaging,	Research Center Juelich, Juelich,	Germany
44.	Franziska	Degenhardt,	Institute of Human Genetics, Department of Genomics, Life and Brain Center,	University of Bonn, Bonn,	Germany
45.	Peter	Falkai,	Department of Psychiatry and Psychotherapy,	Ludwig-Maximilians-University Munich, Munich,	Germany
46.	Oliver	Gruber,	Department of Psychiatry and Psychotherapy,	Georg-August University Göttingen, Göttingen,	Germany
47.	Urs	Heilbronner,	Department of Psychiatry and Psychotherapy,	Georg-August University Göttingen, Göttingen,	Germany
48.	Per	Hoffmann,	Institute of Human Genetics, Department of Genomics, Life and Brain Center,	University of Bonn, Bonn,	Germany
49.	Per	Hoffmann,	Institute of Neuroscience and Medicine (INM-1), Genomic Imaging,	Research Center Juelich, Juelich,	Germany
50.	Sarah	Kittel-Schneider,	Department of Psychiatry, Psychosomatics, and Psychotherapy,	University of Würzburg, Würzburg,	Germany
51.	Markus	Nöthen,	Institute of Human Genetics, Department of Genomics, Life and Brain Center,	University of Bonn, Bonn,	Germany
52.	Andrea	Pfennig,	Department of Psychiatry and Psychotherapy,	University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden,	Germany
53.	Daniela	Reich-Erkelenz,	Department of Psychiatry and Psychotherapy,	Ludwig-Maximilians-University Munich, Munich,	Germany
54.	Andreas	Reif,	Department of Psychiatry, Psychosomatics, and Psychotherapy,	University of Würzburg, Würzburg,	Germany
55.	Marcella	Rietschel,	Department of Genetic Epidemiology in Psychiatry,	Central Institute of Mental Health, Mannheim,	Germany
56.	Thomas G.	Schulze,	Department of Psychiatry and Psychotherapy,	Georg-August University Göttingen, Göttingen,	Germany
57.	Florian	Seemüller,	Department of Psychiatry and Psychotherapy,	Ludwig-Maximilians-University Munich, Munich,	Germany
58.	Thomas	Stamm,	Department of Psychiatry and Psychotherapy,	Charité - Universitätsmedizin Berlin, Campus Charité Mitte, Berlin,	Germany
59.	Raffaella	Ardau,	Unit of Clinical Pharmacology, Hospital University Agency,	University of Cagliari, Cagliari,	Italy
60.	Caterina	Chillotti,	Unit of Clinical Pharmacology, Hospital University Agency,	University of Cagliari, Cagliari,	Italy
61.	Maria	Del Zompo,	Department of Biomedical Sciences,	University of Cagliari, Cagliari,	Italy
62.	Maria	Del Zompo,	Unit of Clinical Pharmacology, Hospital University Agency,	University of Cagliari, Cagliari,	Italy
63.	Mario	Maj,	Department of Psychiatry,	University of Naples, SUN, Naples,	Italy

64.	Mirko	Manchia,	Department of Biomedical Sciences,	University of Cagliari, Cagliari,	Italy
65.	Palmiero	Monteleone,	Department of Psychiatry,	University of Naples, SUN, Naples,	Italy
66.	Giovanni	Severino,	Department of Biomedical Sciences,	University of Cagliari, Cagliari,	Italy
67.	Alessio	Squassina,	Department of Biomedical Sciences,	University of Cagliari, Cagliari,	Italy
68.	Alfonso	Tortorella,	Department of Psychiatry,	University of Naples, SUN, Naples,	Italy
69.	Kazufumi	Akiyama,	Department of Biological Psychiatry and Neuroscience,	Dokkyo Medical University School of Medicine, Mibu,	Japan
70.	Kazufumi	Akiyama,	The Japanese Collaborative Group on the Genetics of Lithium Response in Bipolar Disorder,		Japan
71.	Ryota	Hashimoto,	Molecular Research Center for Children's Mental Development, United Graduate School of Child Development, Osaka University,	Osaka University, Osaka,	Japan
72.	Ryota	Hashimoto,	The Japanese Collaborative Group on the Genetics of Lithium Response in Bipolar Disorder,		Japan
74.	Tadafumi	Kato,	The Japanese Collaborative Group on the Genetics of Lithium Response in Bipolar Disorder,		Japan
75.	Tadafumi	Kato,	Laboratory for Molecular Dynamics of Mental Disorders,	RIKEN Brain Science Institute, Saitama,	Japan
76.	Ichiro	Kusumi,	The Japanese Collaborative Group on the Genetics of Lithium Response in Bipolar Disorder,		Japan
77.	Ichiro	Kusumi,	Department of Psychiatry,	Hokkaido University Graduate School of Medicine, Sapporo,	Japan
78.	Takuya	Masui,	The Japanese Collaborative Group on the Genetics of Lithium Response in Bipolar Disorder,		Japan
79.	Takuya	Masui,	Department of Psychiatry,	Hokkaido University Graduate School of Medicine, Sapporo,	Japan
80.	Norio	Ozaki,	The Japanese Collaborative Group on the Genetics of Lithium Response in Bipolar Disorder,		Japan
81.	Norio	Ozaki,	Department of Psychiatry,	Nagoya University Graduate School of Medicine, Nagoya,	Japan
82.	Piotr	Czerski,	Psychiatric Genetic Unit,	Poznan University of Medical Sciences, Poznan,	Poland
83.	Joanna	Hauser,	Psychiatric Genetic Unit,	Poznan University of Medical Sciences, Poznan,	Poland
84.	Sebastian	Kliwicki,	Department of Adult Psychiatry,	Poznan University of Medical Sciences, Poznan,	Poland

85.	Janusz K.	Rybakowski,	Department of Adult Psychiatry,	Poznan University of Medical Sciences, Poznan,	Poland
86.	Maria	Grigoroiu-Serbanescu,	Biometric Psychiatric Genetics Research Unit,	Alexandru Obregia Psychiatric Hospital, Bucharest,	Romania
87.	Bárbara	Arias,	Department of Biologia Animal, Unitat d'Antropologia, Facultat de Biologia, Universitat de Barcelona, IBUB, CIBERSAM,	Instituto de Salud Carlos III, Barcelona, Catalonia,	Spain
88.	Antonio	Benabarre,	Bipolar Disorders Program, Institute of Neuroscience, Hospital Clinic,	University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia,	Spain
89.	Francesc	Colom,	Bipolar Disorders Program, Institute of Neuroscience, Hospital Clinic,	University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia,	Spain
90.	Esther	Jiménez,	Bipolar Disorders Program, Institute of Neuroscience, Hospital Clinic,	University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia,	Spain
91.	Marina	Mitjans,	Department of Biologia Animal, Unitat d'Antropologia, Facultat de Biologia, Universitat de Barcelona, IBUB, CIBERSAM,	Instituto de Salud Carlos III, Barcelona, Catalonia,	Spain
92.	Eduard	Vieta,	Bipolar Disorders Program, Institute of Neuroscience, Hospital Clinic,	University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia,	Spain
93.	Lena	Backlund,	Department of Molecular Medicine and Surgery,	Karolinska Institutet and Center for Molecular Medicine, Karolinska University Hospital, Stockholm,	Sweden
94.	Lena	Backlund,	Department of Clinical Neuroscience, Centre for Psychiatric Research and Education,	Karolinska Institutet, The Clinic for Affective Disorders, Karolinska University Hospital, Stockholm,	Sweden
95.	Louise	Frisén,	Department of Molecular Medicine and Surgery,	Karolinska Institutet and Center for Molecular Medicine, Karolinska University Hospital, Stockholm,	Sweden
96.	Louise	Frisén,	Department of Clinical Neuroscience, Centre for Psychiatric Research and Education,	Karolinska Institutet, The Clinic for Affective Disorders, Karolinska University Hospital, Stockholm,	Sweden
97.	Catharina	Lavebratt,	Department of Molecular Medicine and Surgery,	Karolinska Institutet and Center for Molecular Medicine, Karolinska University Hospital, Stockholm,	Sweden
98.	Lina	Martinsson,	Department of Molecular Medicine and Surgery,	Karolinska Institutet and Center for Molecular Medicine, Karolinska University Hospital, Stockholm,	Sweden
99.	Lina	Martinsson,	Department of Clinical Neuroscience, Centre for Psychiatric Research and Education,	Karolinska Institutet, The Clinic for Affective Disorders, Karolinska University Hospital, Stockholm,	Sweden
100.	Urban	Ösby,	Department of Molecular Medicine and Surgery,	Karolinska Institutet and Center for Molecular Medicine, Karolinska	Sweden

				University Hospital, Stockholm,	
101.	Martin	Schalling,	Department of Molecular Medicine and Surgery,	Karolinska Institutet and Center for Molecular Medicine, Karolinska University Hospital, Stockholm,	Sweden
102.	Jean-Michel	Aubry,	Départment de Psychiatrie,	HUG - Hôpitaux Universitaires de Genève, Geneva,	Switzerland
103.	Sven	Cichon,	Division of Medical Genetics,	Department of Biomedicine, University of Basel, Basel,	Switzerland
104.	Alexandre	Dayer,	Départment de Psychiatrie,	HUG - Hôpitaux Universitaires de Genève, Geneva,	Switzerland
105.	Alexandre	Dayer,	Department of Basic Neurosciences,	University of Geneva Medical School, Geneva,	Switzerland
106.	Per	Hoffmann,	Division of Medical Genetics,	Department of Biomedicine, University of Basel, Basel,	Switzerland
107.	Audrey	Nallet,	Department of Mental Health and Psychiatry,	Hôpitaux Universitaires de Genéve, Geneva,	Switzerland
108.	Hsi-Chung	Chen,	Department of Psychiatry & Center of Sleep Disorders,	National Taiwan University Hospital, Taipei,	Taiwan
109.	Po-Hsiu	Kuo,	Institute of Epidemiology and Preventive Medicine,	National Taiwan University, Taipei,	Taiwan
110.	David	Cousins,	Campus for Ageing and Vitality,	Newcastle University, Newcastle,	United Kingdom
111.	Nirmala	Akula,	Human Genetics Branch,	National Institute of Mental Health and Human Services, Bethesda, MD,	United States
112.	Joanna M.	Biernacka,	Department of Psychiatry and Psychology,	Mayo Clinic, Rochester, MN,	United States
113.	Joanna M.	Biernacka,	Department of Health Sciences Research,	Mayo Clinic, Rochester, MN,	United States
114.	Elise T.	Bui,	Human Genetics Branch,	National Institute of Mental Health and Human Services, Bethesda, MD,	United States
115.	J. Ray	DePaulo,	Department of Psychiatry and Behavioral Sciences,	Johns Hopkins University, Baltimore, MD,	United States
116.	Sevilla D.	Detera-Wadleigh,	Human Genetics Branch,	National Institute of Mental Health and Human Services, Bethesda, MD,	United States
117.	Mark A.	Frye,	Department of Psychiatry and Psychology,	Mayo Clinic, Rochester, MN,	United States
118.	Fernando S.	Goes,	Department of Psychiatry and Behavioral Sciences,	Johns Hopkins University, Baltimore, MD,	United States
119.	Rebecca	Hoban,	Department of Psychiatry,	University of California San Diego,	United States
120.	Rebecca	Hoban,	Department of Psychiatry,	VA San Diego Healthcare System,	United States
121.	Liping	Hou,	Human Genetics Branch,	National Institute of Mental Health and Human Services, Bethesda, MD,	United States
122.	Layla	Kassem,	Human Genetics Branch,	National Institute of Mental Health and Human Services, Bethesda, MD,	United States
123.	John R.	Kelsoe,	Department of Psychiatry,	University of California San Diego, San Diego, CA,	United States
124.	John R.	Kelsoe,	Department of Psychiatry,	VA San Diego Healthcare System, San Diego, CA,	United States

125.	Gonzalo	Laje,	Human Genetics Branch,	National Institute of Mental Health and Human Services, Bethesda, MD,	United States
126.	Gonzalo	Laje,	Washington Behavioral Medicine Associates, LLC,	Chevy Chase, MD,	United States
127.	Gonzalo	Laje,	Maryland Institute for Neuroscience & Development (MIND),	Chevy Chase, MD,	United States
128.	Susan G.	Leckband,	Department of Psychiatry,	University of California San Diego, San Diego, CA,	United States
129.	Susan G.	Leckband,	Department of Pharmacy,	VA San Diego Healthcare System, San Diego, CA,	United States
130.	Susan G.	Leckband,	Skaggs School of Pharmacy and Pharmaceutical Sciences,	University of California, San Diego, CA,	United States
131.	Michael J.	McCarthy,	Department of Psychiatry,	VA San Diego Healthcare System, San Diego, CA,	United States
132.	Francis J.	McMahon,	Human Genetics Branch,	National Institute of Mental Health and Human Services, Bethesda, MD,	United States
133.	Francis	Mondimore,	Department of Psychiatry and Behavioral Sciences,	Johns Hopkins University, Baltimore, MD,	United States
134.	Roy H.	Perlis,	Department of Psychiatry,	Massachusetts General Hospital and Harvard Medical School, Boston, MA,	United States
135.	James B.	Potash,	Department of Psychiatry,	University of Iowa, Iowa City, IA,	United States
136.	Thomas G.	Schulze,	Department of Psychiatry and Behavioral Sciences,	Johns Hopkins University, Baltimore, MD,	United States
137.	Thomas G.	Schulze,	Human Genetics Branch,	National Institute of Mental Health and Human Services, Bethesda, MD,	United States
138.	Barbara	Schweizer,	Department of Psychiatry and Behavioral Sciences,	Johns Hopkins University, Baltimore, MD,	United States
139.	Lisa R.	Seymour,	Department of Psychiatry,	Mayo Clinic, Rochester, MN,	United States
140.	Jordan W.	Smoller,	Department of Psychiatry,	Massachusetts General Hospital and Harvard Medical School, Boston, MA,	United States
141.	Jo	Steele,	Human Genetics Branch,	National Institute of Mental Health and Human Services, Bethesda, MD,	United States
142.	Sarah	Tighe,	Department of Psychiatry,	University of Iowa, Iowa City, IA,	United States
143.	Peter P.	Zandi,	Department of Mental Health,	Johns Hopkins Bloomberg School of Public Health, Baltimore, MD,	United States

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Curriculum vitae

Personal details

Gender: Male
Date of Birth: 24.12.1987
Nationality: Hungarian
Current Position: physician

Education

2006 - 2010: University of Szeged, English-Hungarian Medical Interpreter and Translator Programme, Szeged, Hungary

2006 - 2012: Medicine, University of Szeged, Faculty of Medicine, Szeged, Hungary *(summa cum laude)*

2017 - 2021: PhD International Max Planck Research School for Translational Psychiatry (IMPRS-TP), Munich, Germany

2018 - 2021: Executive MSc in Health Economics Policy and Management, London School of Economics (LSE), London, UK

Work

2012 - 2014: Graduate researcher, University of Szeged, Department of Psychiatry

04/2014 – 07/2014: Physician, National Institute of Psychiatry and Addictions, Budapest, Hungary

10/2014 – 11/2015: Research fellow, Institute of Psychiatric Phenomics and Genetics, Medical Centre of the University of Munich, Munich, Germany

11/2015 – : Physician, Department of Psychiatry and Psychotherapy & Institute of Psychiatric Phenomics and Genetics, Medical Centre of the University of Munich, Munich, Germany

Munich, 20.08.2021

List of publications

Kalman, J.L., Olde Loohuis L., Vreeker A., [...], Andlauer T.F.M., Schulze T.G., Ophoff R., (2021). Characterization of Age and Polarity at Onset in Bipolar Disorder. *The British Journal of Psychiatry*, in press

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Ruderfer, D.M., Ripke, S., McQuillin, A., [...], **Kalman J.L.,** [...], Wray, N.R., Sklar, P., Kendler, K.S., (2018) Genomic dissection of bipolar disorder and schizophrenia including 28 subphenotypes. *Cell*, 2018 Jun 14;173(7):1705-1715.e16. doi: 10.1016/j.cell.2018.05.046.

LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

Dean's Office
Medical Faculty

MMRS MUNICH MEDICAL RESEARCH SCHOOL

Affidavit

dr. med. Janos Kalmam

Surname, first name

Nußbaumstr. 7.

Street

80366

Zip code, town

Germany

Country

I hereby declare, that the submitted thesis entitled

Genetic characterization of Age and Polarity at Onset in Bipolar Disorder

is my own work. I have only used the sources indicated and have not made unauthorised use of services of a third party. Where the work of others has been quoted or reproduced, the source is always given.

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Munich, 24.03.2022

Place, date

Janos Kalman

Signature doctoral candidate

Confirmation of congruency

LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN | Promotionsbüro Medizinische Fakultät | MMRS

Confirmation of congruency between printed and electronic version of the doctoral thesis

Kalman, Janos

Surname, first name

Nußbaumstraße 7

Street

80336 Munich

Zip code, town, country

I hereby declare, that the submitted thesis entitled:

Genetic Characterization of Age and Polarity at Onset in Bipolar Disorder

is congruent with the printed version both in content and format.

Munich, 20.08.2021

place, date

Janos Kalman

Signature doctoral candidate