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ORIGINAL ARTICLE

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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.

REFERENCES

1. Nöthen MM, Nieratschker V, Cichon S, Rietschel M. New findings in the genetics of major psychoses. *Dialogues Clin Neurosci*. 2010;12:85-93.
2. Zheng J, Erzurumluoglu AM, Elsworth BL, et al. LD Hub: a centralized database and web interface to perform LD score regression that maximizes the potential of summary level GWAS data for SNP heritability and genetic correlation analysis. *Bioinformatics*. 2017;33:272-279.
3. Lichtenstein P, Yip BH, Björk C, et al. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. *Lancet*. 2009;373:234-239.
4. Hou L, Bergen SE, Akula N, et al. Genome-wide association study of 40,000 individuals identifies two novel loci associated with bipolar disorder. *Hum Mol Genet*. 2016;25:3383-3394.
5. Leboyer M, Bellivier F, Nosten-Bertrand M, Jouvent R, Pauls D, Mallet J. Psychiatric genetics: search for phenotypes. *Trends Neurosci*. 1998;21:102-105.
6. McMahon FJ, Stine OC, Chase GA, Meyers DA, Simpson SG, DePaulo JR. Influence of clinical subtype, sex, and lineality on age at onset of major affective disorder in a family sample. *Am J Psychiatry*. 1994;151:210-215.
7. Schulze TG, Alda M, Adli M, et al. The International Consortium on Lithium Genetics (ConLiGen): an initiative by the NIMH and IGSLI to study the genetic basis of response to lithium treatment. *Neuropsychobiology*. 2010;62:72-78.
8. Aminoff SR, Hellvin T, Lagerberg TV, Berg AO, Andreassen OA, Melle I. Neurocognitive features in subgroups of bipolar disorder. *Bipolar Disord*. 2013;15:272-283.
9. Hou L, Heilbronner U, Degenhardt F, et al. Genetic variants associated with response to lithium treatment in bipolar disorder: a genome-wide association study. *Lancet*. 2016;387:1085-1093.
10. Song J, Bergen SE, Di Florio A, et al. Genome-wide association study identifies SESTD1 as a novel risk gene for lithium-responsive bipolar disorder. *Mol Psychiatry*. 2016;21:1290-1297.
11. Propper L, Ortiz A, Slaney C, et al. Early-onset and very-early-onset bipolar disorder: distinct or similar clinical conditions? *Bipolar Disord*. 2015;17:814-820.
12. Kennedy KP, Cullen KR, DeYoung CG, Klimes-Dougan B. The genetics of early-onset bipolar disorder: a systematic review. *J Affect Disord*. 2015;184:1-12.
13. Grigoroiu-Serbanescu M, Rietschel M, Hauser J, et al. Commingling analysis of age-of-onset in bipolar I disorder and the morbid risk for major psychoses in first degree relatives of bipolar I probands. *J Affect Disord*. 2014;168:197-204.
14. Belmonte Mahon P, Pirooznia M, Goes FS, et al. Genome-wide association analysis of age at onset and psychotic symptoms in bipolar disorder. *Am J Med Genet B Neuropsychiatr Genet*. 2011;156B:370-378.
15. Jamain S, Cichon S, Etain B, et al. Common and rare variant analysis in early-onset bipolar disorder vulnerability. *PLoS ONE*. 2014;9:e104326.
16. Craddock N, Sklar P. Genetics of bipolar disorder. *Lancet*. 2013;381:1654-1662.
17. Schizophrenia Working Group of the Psychiatric Genomics Consortium S, Neale BM, Corvin A, et al. Biological insights from 108 schizophrenia-associated genetic loci. *Nature*. 2014;511:421-427.
18. International Schizophrenia Consortium SM, Purcell SM, Wray NR, et al. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature*. 2009;460:748-752.
19. Dudbridge F. Power and predictive accuracy of polygenic risk scores. *PLoS Genet*. 2013;9:e1003348.
20. Aminoff SR, Tesli M, Bettella F, et al. Polygenic risk scores in bipolar disorder subgroups. *J Affect Disord*. 2015;183:310-314.
21. Mühleisen TW, Leber M, Schulze TG, et al. Genome-wide association study reveals two new risk loci for bipolar disorder. *Nat Commun*. 2014;5:3339.
22. Psychiatric GWAS Consortium Bipolar Disorder Working Group P, Ripke S, Scott LJ, et al. Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. *Nat Genet*. 2011;43:977-983.
23. Budde M, Anderson-Schmidt H, Gade K, et al. A Longitudinal Approach to Biological Psychiatric Research: The PsyCourse Study. Preprints, 2017.
24. Andlauer TFM, Buck D, Antony G, et al. Novel multiple sclerosis susceptibility loci implicated in epigenetic regulation. *Sci Adv*. 2016;2:e1501678.
25. Fuchsberger C, Abecasis GR, Hinds DA. minimac2: faster genotype imputation. *Bioinformatics*. 2015;31:782-784.
26. Delaneau O, Zagury J-F, Marchini J. Improved whole-chromosome phasing for disease and population genetic studies. *Nat Methods*. 2013;10:5-6.
27. Purcell S, Neale B, Todd-Brown K, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet*. 2007;81:559-575.
28. Carlson GA, Pataki C. Understanding early age of onset: a review of the last 5 years. *Curr Psychiatry Rep*. 2016;18:114.
29. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna: R Foundation for Statistical Computing; 2015.
30. Gottesman II, Shields J. A polygenic theory of schizophrenia. *Proc Natl Acad Sci USA*. 1967;58:199-205.

31. Lin P-I, McInnis MG, Potash JB, et al. Clinical correlates and familial aggregation of age at onset in bipolar disorder. *Am J Psychiatry*. 2006;163:240-246.
32. Post RM, Leverich GS, Kupka R, et al. Increased parental history of bipolar disorder in the United States: association with early age of onset. *Acta Psychiatr Scand*. 2014;129:375-382.

SUPPORTING INFORMATION

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

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