Genetic characterization of age and polarity at onset in bipolar disorder

Supplementary Material

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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.

euoI | 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	PsychChip	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.

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