Data supplement for Zwicker et al., Polygenic Scores and Onset of Major Mood or Psychotic Disorders Among Offspring of Affected Parents. Am J Psychiatry (doi: 10.1176/appi.ajp.20220476)

1. Supplementary Methods

1.1. Study-specific inclusion and exclusion criteria

Families Overcoming Risks and Building Opportunities for Well-being study (FORBOW) (1). All biological offspring in the eligible age range (3 to 21 years at baseline) were included in this study, provided that at least one of their biological parents was available for assessment and that the offspring or their legal guardian provided valid informed consent. Multiple offspring from the same family were included, when available. Exclusion criteria were acquired brain injury or intellectual disability of a degree that made all or most assessments invalid. Offspring with milder intellectual disability, autism or attention-deficit hyperactivity disorder were included.

Maritime Bipolar Family Study (MBFS) (2). We included the offspring of parents with bipolar disorder who participated in genetic linkage studies of bipolar disorder (3). We included offspring aged 15 to 30 years at the time of their first assessment. Multiple offspring from the same family were included, when available. Exclusion criteria were acquired brain injury or intellectual disability of a degree that made all or most assessments invalid. Control participants were screened unaffected population controls.

Bipolar and Schizophrenia Young Offspring Study (BASYS) (4). Inclusion criteria for the offspring of parents with schizophrenia and the offspring of parents with bipolar disorder were as follows: 1) age between 6 and 17 years and 2) biological parent diagnosed with bipolar disorder or

schizophrenia. Exclusion criteria for offspring of parents with schizophrenia and offspring of parents with bipolar disorder were as follows: 1) intellectual disability and 2) significant head injury or current medical or neurological condition. The only inclusion criterion for the offspring of controls was age between 6 and 17 years, while the exclusion criteria were the same as for the high-risk group, plus a first- or second-degree family history of psychotic disorder. There were no significant differences between participants who did and did not contribute genetic samples in terms of sex, socioeconomic status, or age.

Early Prediction of Adolescent Depression study (EPAD) (5). We included the adolescent offspring of parents with a history of recurrent unipolar major depressive disorder. Parents were screened over the phone prior to participation to ensure that they met the following inclusion criteria: 1) parent has experienced at least 2 episodes of unipolar depression, 2) parent was living with their 9–17-year-old biological offspring. If there was more than 1 child in the home willing to participate, the youngest child in the eligible age range was selected. There were no diagnostic exclusion criteria for the offspring. Because of potential difficulties in completing study assessments, families where the participating child had moderate to severe intellectual disability (IQ < 50) were excluded.

Dutch Bipolar and Schizophrenia Offspring Study (DBSOS) (6). We included only Dutch speaking offspring. Inclusion criteria for family high-risk offspring were at least 1 first-degree or 2 second-degree relatives affected with bipolar disorder or schizophrenia. Exclusion criteria for both high-risk and control participants were as follows: 1) severe physical illness, disability, or neurological

problems (e.g., open- or closed-head injury, epilepsy), and 2) IQ < 70. Controls were excluded if they had a first-degree relative with a severe mood or psychotic disorder.

Sydney Bipolar Kids and Sibs study (BK&S) (7). Affected parents had a diagnosis of bipolar disorder, type I, bipolar disorder, type II with recurrent major depression or schizoaffective disorder, bipolar type. Exclusion criteria for control parents included: 1) bipolar disorder type I or II, 2) recurrent major depression, 3) schizoaffective disorder or schizophrenia, 4) a first- or second-degree relative with a history of psychosis, or 5) a first- or second-degree relative with a psychiatric hospitalization. All available offspring of affected and control parents were included.

Pittsburgh Bipolar Offspring Study (BIOS) (8). Inclusion criteria for the parents with bipolar disorder were as follows: 1) diagnosis of bipolar disorder type I or II (at intake and maintained over follow-up) and 2) having offspring aged 6-18 years old. Exclusion criteria for parents with bipolar disorder were as follows: 1) current or lifetime diagnosis of schizophrenia, 2) IQ < 70, 3) mania or hypomania secondary to substance use, medical conditions, or medication use and 4) not able to cooperate with interviews. Community control parents with offspring aged 6-18 years were included if they were healthy or had non-bipolar disorder psychopathology. Exclusion criteria for community control parents were as follows: 1) having a spouse with bipolar disorder, 2) having a first- or second-degree family history of bipolar disorder, 3) IQ < 70, and 4) not able to cooperate with interviews. All offspring of parents with bipolar disorder and community controls were recruited, unless they met the following exclusion criteria: 1) IQ < 70, 2) autism spectrum disorder diagnosis, 3) presence of conditions that interfered with the evaluation, and 4) living more than 200 miles away from Pittsburgh, Pennsylvania.

USA Bipolar High-Risk Project (USAB) (9). Probands (parents or siblings) had a lifetime DSM-IV diagnosis of bipolar disorder type I, bipolar disorder type II with recurrent major depression, or schizoaffective disorder, bipolar type. Second-degree relatives were included only when the family was multiplex. Exclusion criteria for control parents were a diagnosis of bipolar disorder (I or II), recurrent major depression, schizoaffective disorder, or schizophrenia in either parent.

1.2. Assessment of parent psychopathology

Families Overcoming Risks and Building Opportunities for Well-being study (FORBOW) (1). Diagnoses of mental disorders according to the Diagnostic and Statistical Manual IV (DSM-IV) and DSM-5 were established using the Schedule for Affective Disorders and Schizophrenia (SADS-IV) (10) and the Structured Clinical Interview for DSM-5 Disorders (SCID-5) (11). Diagnoses were confirmed in consensus meetings with a psychiatrist blind to offspring psychopathology.

Maritime Bipolar Family Study (MBFS) (2). Diagnoses of mental disorders according to the Diagnostic and Statistical Manual IV (DSM-IV) were established using the Schedule for Affective Disorders and Schizophrenia (SADS-IV) (10). Diagnoses were confirmed in consensus meetings with at least two additional psychiatrists blind to offspring psychopathology.

Bipolar and Schizophrenia Young Offspring Study (BASYS) (4). Diagnoses of mental disorders according to DSM-IV were established using the Spanish version of the Structured Clinical Interview for DSM-IV Disorders (SCID-IV), administered by a trained psychiatrist (11).

Early Prediction of Adolescent Depression study (EPAD) (5). Parents were screened over the telephone to ensure that they met diagnostic inclusion criteria. Parents were required to have experienced recurrent unipolar depression (2+ episodes) but were not required to be experiencing a depressive episode at the time of recruitment. Diagnoses were confirmed by diagnostic interview. We assessed the index parent's psychiatric state over the month prior to inclusion using the Schedules for Clinical Assessment in Neuropsychiatry (12). A timeline of the affected parent's previous depressive episodes was compiled using a life history calendar approach. Parents with a psychotic or bipolar diagnosis and those who met DSM-IV criteria for mania/hypomania at the time of interview were excluded from the study.

Dutch Bipolar and Schizophrenia Offspring Study (DBSOS) (6). DSM-IV criteria for bipolar I or II disorder or psychotic disorders were verified by applying the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (11) in interviews with the affected parent and the mini-Schedule for Clinical Assessment in Neuropsychiatry (mini-SCAN), followed by a SCID-I in case of reported psychopathology, with their partner (if available).

Sydney Bipolar Kids and Sibs study (BK&S) (7). Parents were initially assessed using the Family Interview for Genetic Studies (FIGS) (13) to determine a family history of bipolar disorder. At least one parent of each participant completed the FIGS. Parents were then assessed for DSM-IV disorders using the Diagnostic Interview for Genetic Studies and the Family Instrument for Genetic Studies (http: //www.nimhgenetics.org).

Pittsburgh Bipolar Offspring Study (BIOS) (8). Diagnoses of mental disorders according to the DSM-IV were established using the Structured Clinical Interview for DSM-IV Disorders (SCID-IV) (11).

USA Bipolar High-Risk Project (USAB) (9). Probands were assessed for DSM-IV disorders using the Diagnostic Interview for Genetic Studies (14) and the Family Instrument for Genetic Studies (http: //www.nimhgenetics.org).

1.3. Recruitment and assessment of offspring psychopathology

Families Overcoming Risks and Building Opportunities for Well-being study (FORBOW) (1). Parents were identified through inpatient and outpatient psychiatric services in Nova Scotia, Canada. Clinicians systematically inquired whether patients with psychotic and major mood disorders (schizophrenia, schizoaffective disorder, bipolar disorder, major depressive disorder) had children below the age of 21 years. The youth participants were ascertained through parents and recruited regardless of whether any psychopathology was present in the offspring. Offspring were assessed annually for mental disorders using the Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime Version (K-SADS-PL both self- and parent-report; all baseline assessments and in offspring younger than 18 years) (15) or the Structured Clinical Interview for DSM-5 (SCID; in follow-ups of offspring 18+ years old) (11). Offspring assessors were blind to parent psychopathology. Diagnoses were confirmed in consensus meetings with a psychiatrist blind to parent diagnoses.

Maritime Bipolar Family Study (MBFS) (2). The families were identified through probands' (parent or grandparent) contact with mental health services in Nova Scotia, Canada. Control families were recruited through local advertisements. Individuals who were younger than 30 years of age and who were not affected at baseline were included in the present study. Best estimate diagnoses were confirmed in consensus meetings with psychiatrists blind to diagnoses of family members, using all available information obtained through the K-SADS-PL (15) for participants up to age 18 years or the SADS-L and the Diagnostic Interview for Genetic Studies (DIGS) (14) for participants older than 18 years.

Bipolar and Schizophrenia Young Offspring Study (BASYS) (4). Parents were identified through their contact with hospital psychiatrists. Clinicians inquired whether patients with bipolar disorder or schizophrenia had 6-17 year old offspring. Youth participants were ascertained through parents, regardless of whether psychopathology was present in the offspring. A control group was recruited through advertisements posted in primary health care centres and other community locations within the same geographical area. Offspring were assessed for mental disorders by child psychiatrists blind to parent diagnoses using the Spanish version of the K-SADS-PL (both self- and parent-report) (15).

Early Prediction of Adolescent Depression study (EPAD) (5). Parents with recurrent major depressive disorder were recruited though general medical practices across South Wales, UK (78%), through a database of individuals with unipolar depression (19%), or through advertisements in local media and primary care centres (3%). Parents were included if they experienced recurrent unipolar DSM-IV major depressive disorder (at least 2 episodes), confirmed

by diagnostic interview using the Schedule for Clinical Assessment in Neuropsychiatry (SCAN). Offspring aged 9-17 years who resided with their biological parent were included. If more than 1 child per household was willing to participate, only the youngest eligible child was selected. Offspring were assessed for mental disorders using the parent and child versions of the Child and Adolescent Psychiatric Assessment (CAPA) (16). All cases that met criteria for diagnosis or those with subthreshold symptoms were reviewed by 2 child psychiatrists and diagnoses were confirmed by clinical consensus.

Dutch Bipolar and Schizophrenia Offspring Study (DBSOS) (6). Offspring (aged 8-18 years old) of parents with schizophrenia or bipolar disorder were recruited via their psychiatrist from the University Medical Center Utrecht or other mental health care centers in the Netherlands (28.3%), their parent's or sibling's psychiatrist (37.7%), or through advertisement (34%; *e.g.*, lectures, patient advocacy groups and study website). Control offspring were recruited via advertisement on schools or leisure clubs (57.5%), or via hospital staff (42.5%). Offspring were assessed for mental disorders using the K-SADS-PL (both self- and parent-report; at baseline and 4-year follow-up) (11,15). Diagnoses were evaluated by psychiatrists and confirmed by clinical consensus.

Sydney Bipolar Kids and Sibs study (BK&S) (7). Parents with bipolar disorder were recruited through their participation in bipolar disorder pedigree studies, a specialized bipolar disorder research clinic, clinicians, mental health consumer organizations, and advertisements. Control parents were recruited via print and electronic media in universities and local communities. Offspring aged 12-21 years were assessed for mental disorders using the K-SADS-BP, both self-

and parent-report (9,15). Offspring > 21 years old were assessed for present and lifetime diagnoses using the Diagnostic Interview for Genetic Studies (DIGS) (14). Offspring consensus diagnoses were determined by 2 independent raters using best estimate methodology.

Pittsburgh Bipolar Offspring Study (BIOS) (8). Parents with bipolar disorder were recruited through advertisement, adult bipolar disorder studies, and outpatient clinics in Pittsburgh, Pennsylvania, USA. Parents were required to fulfill DSM-IV criteria for bipolar disorder type I or II. Control parents consisted of healthy parents or parents with non-bipolar disorder psychiatric disorders from the community and were group matched by age, sex, and neighborhood. All willing offspring aged 6 to 18 years from each family were included in the study. Offspring were assessed for mental disorders using the K-SADS-PL, both self- and parent-report (15). Offspring assessors were blind to parent psychopathology. Diagnoses were confirmed in consensus meetings with a psychiatrist blind to parent diagnoses.

USA Bipolar High-Risk Project (USAB) (9). Parents were included from 4 collection sites: Indiana University School of Medicine, Indianapolis, USA (coordinating site); University of Michigan, Ann Arbor, USA; The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; and Washington University at St Louis, St Louis, Missouri, USA. Affected parents were all in treatment (outpatient or inpatient) at the time of ascertainment. Affected parents had a diagnosis of bipolar disorder, type I, bipolar disorder, type II with recurrent major depression or schizoaffective disorder, bipolar type. Control parents were recruited through general medicine clinics, motor vehicle records, and campus advertising. Exclusion criteria for control parents included bipolar disorder type I or II, recurrent major depression, schizoaffective disorder,

schizophrenia in either parent, or parents with a first-degree relative with a psychiatric hospitalization. All offspring aged 12-21 years were invited to participate. Offspring were assessed for mental disorders using the K-SADS-BP (9,15), both self- and parent-report. Offspring assessors were blind to the specific hypotheses of the study. Diagnoses were determined by consensus between 2 clinicians who were blind to parent diagnoses.

1.4. Genotyping

The collection of biological samples and genotyping platforms used were as follows:

Families Overcoming Risks and Building Opportunities for Well-being study (FORBOW) (1). We extracted genomic DNA from saliva collected via the Oragene kit (DNA Genotek Inc, Kanata, ON). All DNA samples were quantified using the Nanodrop spectrophotometer and DNA quality was evaluated using 260/280 ratios. We genotyped single nucleotide polymorphisms (SNPs) using the Illumina's Global Screening Array (Illumina, San Diego, CA) at The Center for Applied Genomic, The Hospital for Sick Children, Toronto, Canada.

Maritime Bipolar Family Study (MBFS). Blood samples obtained by venipuncture were shipped by overnight courier to Dr. Rouleau's laboratory at McGill University and DNA was isolated as previously reported (2). Genotyping was completed in two batches, one at The Center for Applied Genomic, The Hospital for Sick Children, Toronto, and the other one at McGill Genome Centre, Montreal, Canada. Both used the Illumina's Global Screening Array (Illumina, San Diego, CA).

Bipolar and Schizophrenia Young Offspring Study (BASYS) (4). Genomic DNA was extracted from saliva samples collected via the Oragene kit and from blood samples using the MagNA Pure LC system (Roche). All DNA samples were quantified using the Nanodrop spectrophotometer and DNA quality was evaluated using 260/280 ratios. Common SNPs were genotyped using Affymetrix Axiom® matrix plates (Axiom Spain BA).

Early Prediction of Adolescent Depression study (EPAD) (5). Genomic DNA was extracted from saliva samples collected via the Oragene kit (DNA Genotek Inc, Kanata, ON). DNA was genotyped in-house using Illumina 'Infinium Psych Array' custom chips and the hg19+1 genome build by the core team at the MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University.

Dutch Bipolar and Schizophrenia Offspring Study (DBSOS) (17). Genomic DNA was extracted from whole blood. Genotype data were generated using the Illumina HumanOmniExpressExome-8 v1.2 on Illumina's 550K platform.

Sydney Bipolar Kids and Sibs study (BK&S) (7). Genomic DNA was extracted from whole blood by Genetic Repositories Australia (Sydney, NSW, Australia) , as previously described (18). Genome-wide SNP genotyping was conducted together with USAB samples, using the Infinium PsychArray BeadChip at the Mt. Sinai School of Medicine Genomics Core Facility, as previously described (18).

Pittsburgh Bipolar Offspring Study (BIOS) (8). We extracted genomic DNA from saliva samples using Puregene DNA extraction kits at the University of Pittsburgh Medical Center. We genotyped DNA samples at the Genomics Research Core at the Children's Hospital of Philadelphia using Illumina's Global Screening Array (Illumina, San Diego, CA).

USA Bipolar High-Risk Project (USAB) (9). Genomic DNA was extracted from whole blood by the Rutgers University Cell and DNA Repository (New Brunswick, NJ), as previously described (18). Genome-wide SNP genotyping was conducted was conducted together with BK&S samples using the Infinium PsychArray BeadChip at the Mt. Sinai School of Medicine Genomics Core Facility, as previously described (18).

1.5. Genetic quality control and imputation

We completed pre-imputation quality control on genome-wide data from each individual cohort separately by excluding variants and participants according to the following criteria: 1) variants with minor allele frequency less than 1%; 2) variants with missing rate greater than 5%; 3) participants with genotyping rate less than 95%; 4) variants with significant deviations from Hardy-Weinberg equilibrium ($p < 10 \times 10^{-10}$); 5) participants with discrepancies between self-reported sex and genetic sex; 6) participants with abnormally high genome-wide heterozygosity (> 4 SD above sample mean); 7) participants with self-reported non-European ancestry; and 8) participants who were outliers on the top 4 ancestry informative principal components (> 4 SD above or below sample mean), see Table S3. Additional genotypes were imputed using Minimac4 via the Michigan Imputation Server (https://imputationserver.sph.umich.edu). Post-imputation, we pruned variants with minor allele frequency less than 1% and with poor imputation quality (R^2 <

0.80). Cohorts were merged post-imputation using PLINK (19). Following cohort merging, we excluded variants with genotyping rate < 95% or minor allele frequency < 1% in the full sample.

1.6.Testing associations between PGS and familial high-risk status

We tested associations between polygenic scores and family history of mood and psychotic disorders using logistic regression. We used robust standard error to account for the non-independence of observations from related individuals ('sandwich' and 'lmtest' packages). All models accounted for sex, age at first assessment, age at last assessment, and genetic population structure indexed with 10 genetic principal components. Associations were quantified as odds ratios. Analyses were implemented in R Studio (R version 4.0.1).

2. Supplementary Results

2.1. Associations between PGS and familial high-risk status

Higher PGS for multiple phenotypes were associated with familial high-risk status. After accounting for sex, age at first assessment, age at last assessment, and ancestry informative principal components, higher PGS for bipolar disorder (OR = 1.40, 95% CI 1.26 to 1.56, $p < 0.001$), p-factor (OR = 1.35, 95% CI 1.22 to 1.49, $p < 0.001$), neuroticism (OR = 1.31, 95% CI 1.18 to 1.45, $p < 0.001$), major depression (OR = 1.25, 95% CI 1.13 to 1.38, $p < 0.001$), schizophrenia (OR = 1.22, 95% CI 1.10 to 1.35, $p < 0.001$), ADHD (OR = 1.15, 95% CI 1.04 to 1.27, $p = 0.005$), and anxiety (OR = 1.13, 95% CI 1.02 to 1.25, $p = 0.012$) were significantly positively associated with family history of illness (Figure S2). PGS for height and subjective well-being were not significantly associated with familial high-risk status.

2.2. Schoenfeld residuals tests

We tested the proportional hazards assumption of models examining the association between PGS and onset of major mood or psychotic disorders. For all models tested, we found a non-significant relationship between residuals and time for each individual PGS and the global test for each full model, indicating that we can assume proportional hazards for each of these models (Figure S6).

2.3. Sensitivity analyses restricted to individuals followed-up until age 15 years or older

The majority of the sample (73.6%, N = 1387) was followed up until age 15 years or older. When we restricted our analyses to this subset of individuals, our main results were confirmed. All effect sizes were within 1 standard error of the original finding and most retained statistical significance. Higher polygenic scores for multiple phenotypes remained associated with onset of mood and

psychotic disorders. After accounting for age, follow-up duration, sex and genetic principal components, PGS for neuroticism (HR 1.23, 95% CI 1.11 to 1.36, $p < 0.001$), schizophrenia (HR 1.13, 95% CI 1.02 to 1.26, $p = 0.015$), depression (HR 1.14, 95% CI 1.03 to 1.27, $p = 0.010$), and p-factor (HR 1.17, 95% CI 1.06 to 1.29, $p = 0.002$) were positively associated with onset of major mood and psychotic disorders. PGS for ADHD was directionally positively associated with illness onset, but this was not statistically significant (HR 1.10, 95% CI 0.99 to 1.21, $p = 0.072$). PGS for subjective well-being was directionally negatively associated with illness onset, but this was not statistically significant (HR 0.92, 95% CI 0.83 to 1.01, $p = 0.089$). As expected, height PGS was not associated with disorder onset (HR 0.95, 95% CI 0.86 to 1.06, $p = 0.350$). PGS for neuroticism, subjective well-being, and p-factor were significantly associated with onsets of major mood and psychotic disorders, independent of family history of these disorders. After accounting for family history, neuroticism PGS (HR 1.19, 95% CI 1.07 to 1.32, $p = 0.001$) and p-factor PGS (HR 1.11, 95% CI 1.01 to 1.23, $p = 0.039$) were positively associated with onsets of major mood and psychotic disorders and subjective well-being PGS remained negatively associated with onsets of these disorders (HR 0.90, 95% CI 0.81 to 0.90, $p = 0.044$).

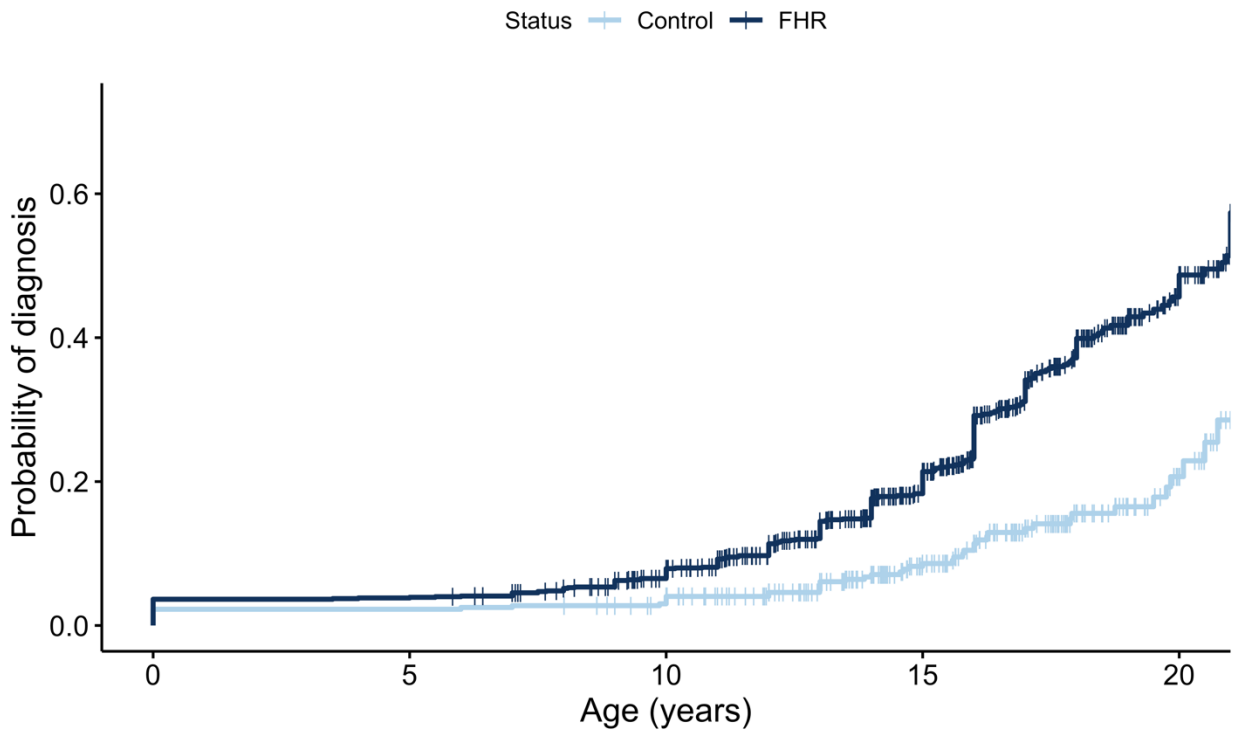
2.4. Sensitivity analyses controlling for study

To control for potential confounding due to heterogeneity across the individual studies included in our sample, we excluded participants drawn from the study that consists only of offspring of parents with major depressive disorder (EPAD) and we repeated our primary analyses with ‘study’ included as a covariate in the models. When we exclude participants from the EPAD and adjust for study, our main results were confirmed. All effect sizes were within 1 standard error of the original finding and most retained statistical significance. Higher polygenic scores for multiple

phenotypes remained associated with onset of mood and psychotic disorders. After accounting for age, follow-up duration, sex, study, and genetic principal components, PGS for neuroticism (HR 1.25, 95% CI 1.13 to 1.39, $p < 0.001$), schizophrenia (HR 1.14, 95% CI 1.03 to 1.26, $p = 0.015$), depression (HR 1.14, 95% CI 1.03 to 1.26, $p = 0.012$), ADHD (HR 1.12, 95% CI 1.01 to 1.24, $p = 0.027$), and p-factor (HR 1.16, 95% CI 1.05 to 1.29, $p = 0.003$) remained positively associated with onset of major mood and psychotic disorders. PGS for subjective well-being remained negatively associated with illness onset (HR 0.90, 95% CI 0.82 to 0.99, $p = 0.048$). As expected, height PGS was not associated with disorder onset (HR 0.96, 95% CI 0.87 to 1.06, $p = 0.430$). PGS for neuroticism, subjective well-being, and p-factor were significantly associated with onsets of major mood and psychotic disorders, independent of family history of these disorders. After accounting for family history, neuroticism PGS (HR 1.22, 95% CI 1.10 to 1.35, $p < 0.001$) remained positively associated with onsets of major mood and psychotic disorders and subjective well-being PGS remained negatively associated with onsets of these disorders (HR 0.89, 95% CI 0.80 to 0.99, $p = 0.026$).

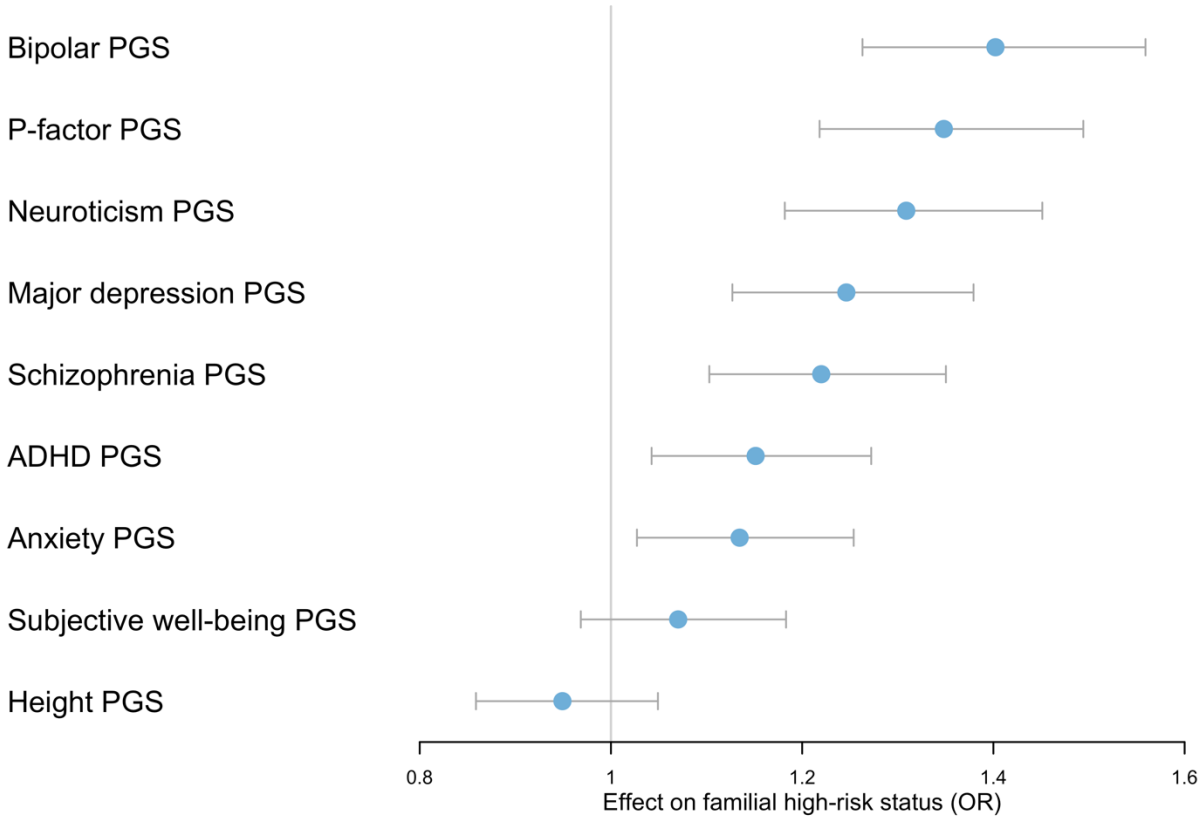
3. Supplementary Figures and Tables

FIGURE S1. The relationship between family high-risk status and onsets of major mood or psychotic disorders



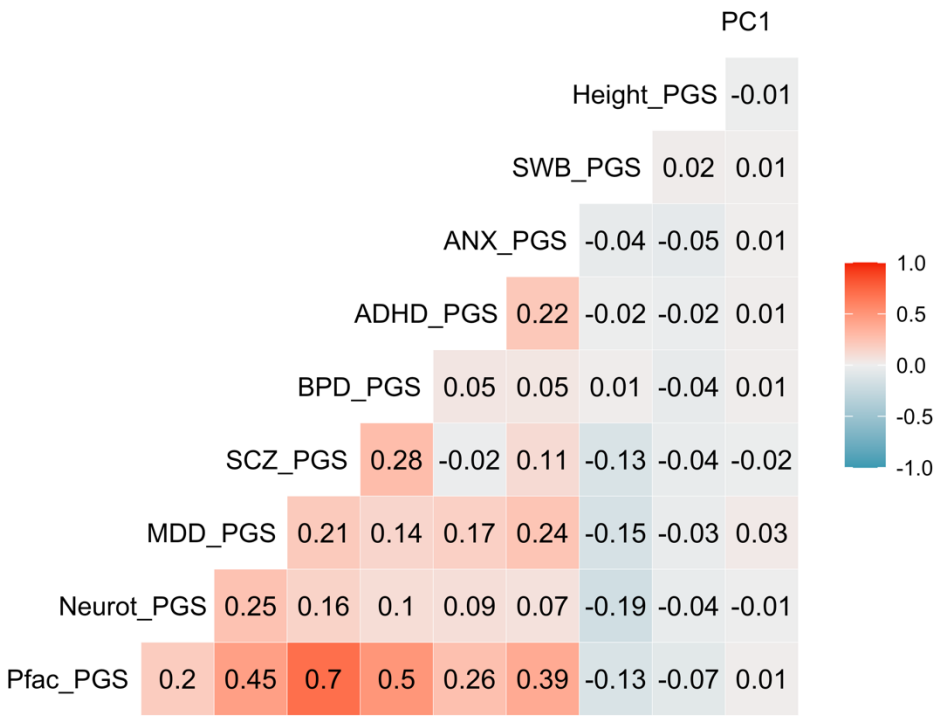
Number at risk					
	0 years	**5 years**	**10 years**	**15 years**	**20 years**
Control	399	390	378	232	50
FHR	1124	1081	1016	612	89

FIGURE S2. Relationships between polygenic scores and family history of major mood or psychotic disorders, quantified as odds ratios



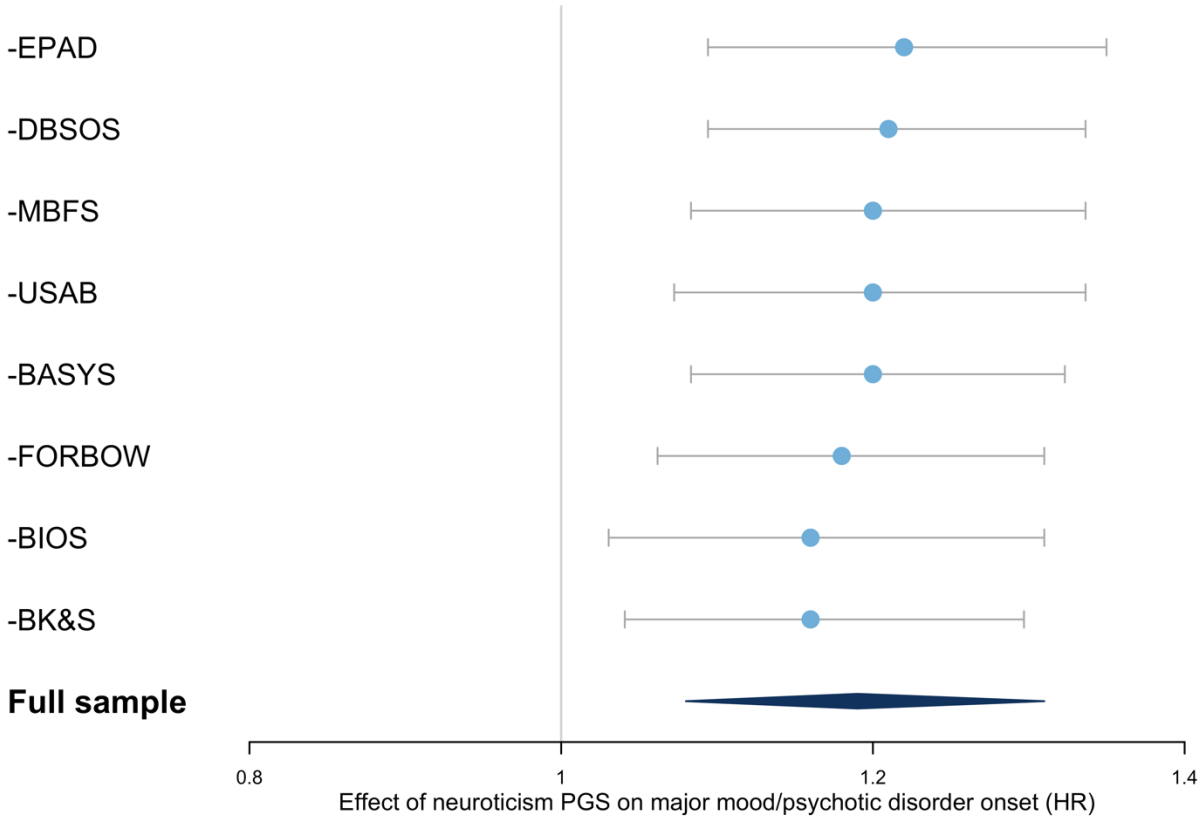
OR = Odds ratio; Bars represent confidence intervals corresponding to α = 0.05.

FIGURE S3. Correlation matrix showing relationships between genetic variables. The numbers within the boxes represent Pearson correlation coefficients. All polygenic scores are residualized to account for the effect of the top 10 ancestry informative principal components. Polygenic scores are shown at the p-value threshold that maximally captured phenotypic variance in the discovery GWAS.



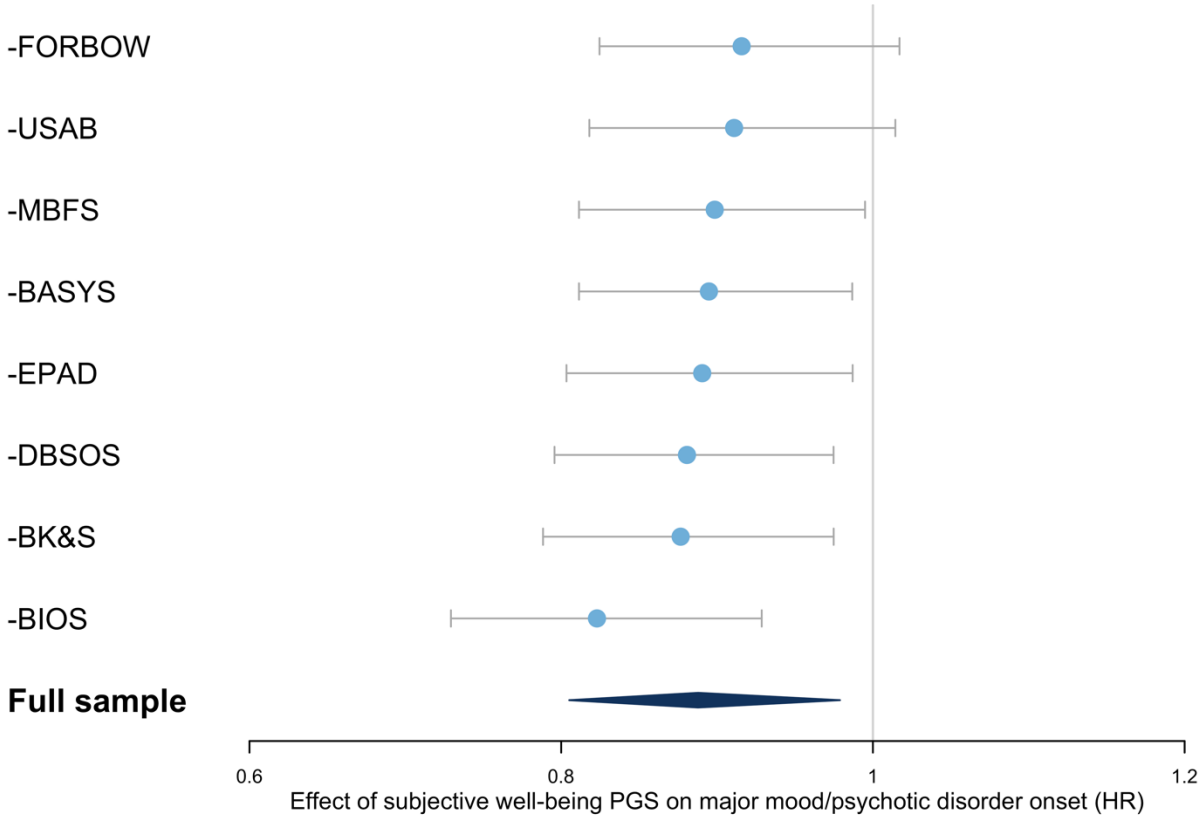
Pfac_PGS = P-factor PGS; Neurot_PGS = neuroticism PGS; MDD_PGS = major depressive disorder PGS; SCZ_PGS = schizophrenia PGS; BPD_PGS = bipolar disorder PGS; ADHD_PGS = attention-deficit/hyperactivity disorder PGS; ANX_PGS = anxiety disorders PGS; SWB_PGS = subjective well-being PGS; Height_PGS = height PGS; PC1 = top ancestry informative principal component.

FIGURE S4. Leave-one-out analyses showing the effect of neuroticism PGS on onsets of major mood or psychotic disorders, after controlling for family history. The cohort that was excluded is shown on the y-axis.



HR = Hazard ratio; Bars represent confidence intervals corresponding to α = 0.05. BASYS = Bipolar and Schizophrenia Young Offspring Study; FORBOW = Families Overcoming Risks and Building Opportunities for Well-being study; EPAD = Early Prediction of Adolescent Depression study; USAB = USA Bipolar High-Risk Project; DBSOS = Dutch Bipolar and Schizophrenia Offspring Study; BK&S = Sydney Bipolar Kids and Sibs study; BIOS = Pittsburgh Bipolar Offspring Study; MBFS = Maritime Bipolar Family Study.

FIGURE S5. Leave-one-out analyses showing the effect of subjective well-being PGS on onsets of major mood or psychotic disorders, after controlling for family history. The cohort that was excluded is shown on the y-axis.



HR = Hazard ratio; Bars represent confidence intervals corresponding to α = 0.05. BASYS = Bipolar and Schizophrenia Young Offspring Study; FORBOW = Families Overcoming Risks and Building Opportunities for Well-being study; EPAD = Early Prediction of Adolescent Depression study; USAB = USA Bipolar High-Risk Project; DBSOS = Dutch Bipolar and Schizophrenia Offspring Study; BK&S = Sydney Bipolar Kids and Sibs study; BIOS = Pittsburgh Bipolar Offspring Study; MBFS = Maritime Bipolar Family Study.

FIGURE S6. Schoenfeld residuals test results. The global Schoenfeld residual test p-value represents the p-value for the residuals test of the full model and the Schoenfeld individual test p-value represents the p-value for each individual PGS. P-values for each of the global test and individual test that are > 0.05 indicate that the proportional hazards assumption was not violated.

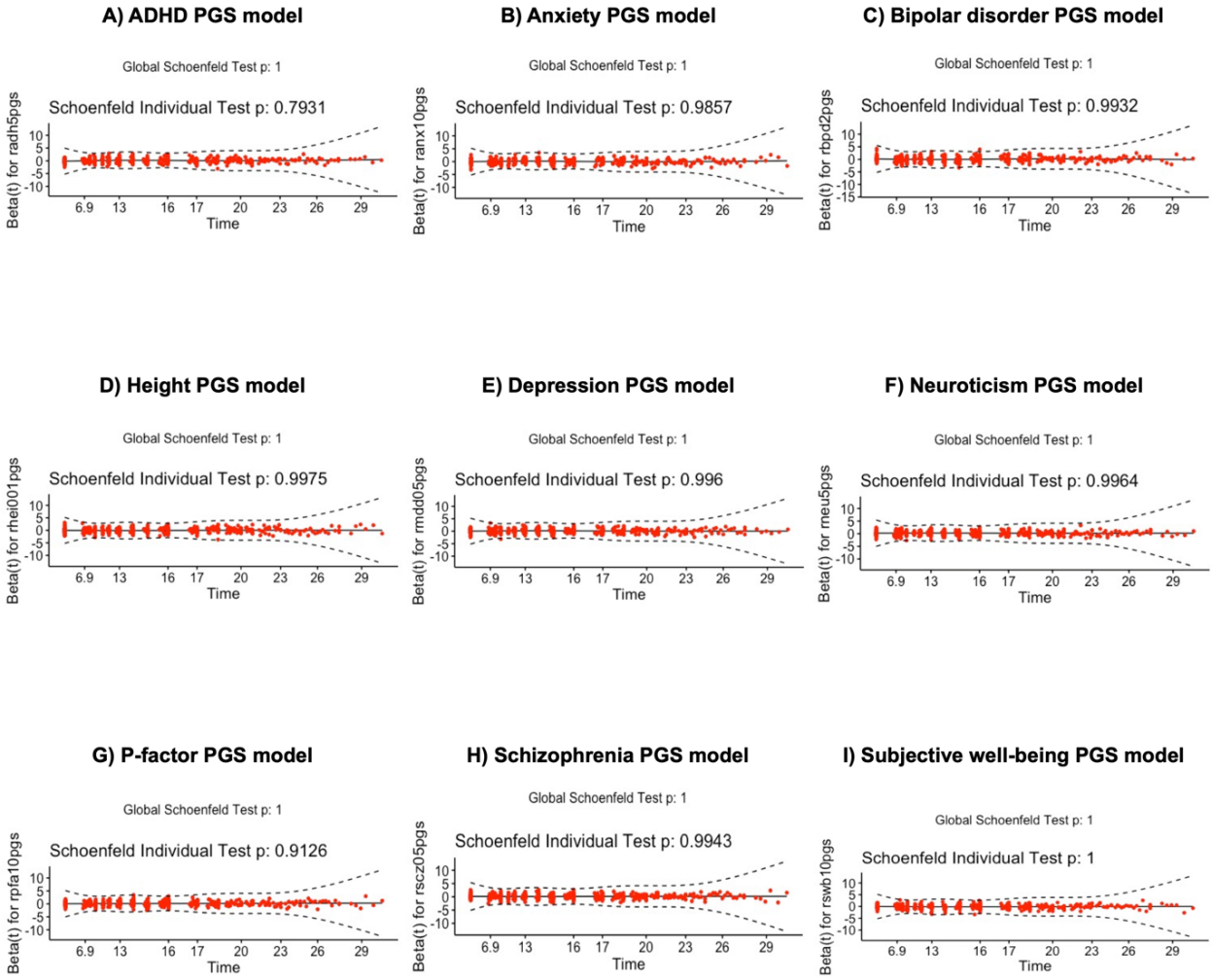


TABLE S1. The sample sizes of the discovery GWAS, after removal of subsets that included relatives in the present study, from which summary statistics were used to construct the PGS in our study

Phenotype	Sample size
ADHD (20)	53,293
Anxiety disorders (21)	31,880
Bipolar disorder (22)	42,984
Height (23)	693,529
Major depressive disorder (24)	173,005
Neuroticism (25)	390,278
Schizophrenia (26)	105,318
Subjective well-being (27)	204,966

TABLE S2. The number of SNPs included in each polygenic score at the p-value threshold that was used in analyses. P_T = p-value threshold for SNP inclusion

Polygenic score	Number of SNPs included
ADHD	
P_T = 0.50	94801
Anxiety disorders	
P_T = 1.00	105991
Bipolar disorder	
P_T = 0.10	33967
Height	
P_T = 0.001	16691
Major depressive disorder	
P_T = 0.05	23558
Neuroticism	
P_T = 0.50	123571
P-factor	
P_T = 1.00	142402
Schizophrenia	
P_T = 0.05	36222
Subjective well-being	
P_T = 1.00	91719

TABLE S3. The number of genetic quality control participant exclusions, stratified by cohort

Criterion	BASYS	FORBOW	EPAD	USAB	DBSOS	BK&S	BIOS	MBFS
Low genotyping rate	0	2	3	2	0	17	87	12
Sex mismatch	0	1	3	3	0	0	4	1
High heterozygosity	0	0	0	0	0	0	0	0
Non-European ancestry	0	13	0	53	0	10	174	1
PCA outlier	29	16	7	21	18	47	12	40

Low genotyping rate refers to a genotyping rate < 95%; sex mismatch refers to a discrepancy between self-reported sex and genetic sex; high heterozygosity refers to genome-wide heterozygosity > 4 SD above the sample mean; non-European ancestry refers to self-reported ethnicity that is non-European; PCA outlier refers to value > 4 SD above sample mean on any of the top 4 genetic principal components. BASYS = Bipolar and Schizophrenia Young Offspring Study; FORBOW = Families Overcoming Risks and Building Opportunities for Well-being study; EPAD = Early Prediction of Adolescent Depression study; USAB = USA Bipolar High-Risk Project; DBSOS = Dutch Bipolar and Schizophrenia Offspring Study; BK&S = Sydney Bipolar Kids and Sibs study; BIOS = Pittsburgh Bipolar Offspring Study; MBFS = Maritime Bipolar Family Study.

TABLE S4. Variance in time until diagnosis of major mood or psychotic disorder explained by fixed effects in each model. All models account for age, follow-up duration, sex and genetic principal components and include family identifier as a random effect. The multivariate PGS model contains PGS for neuroticism, schizophrenia, p-factor, depression, ADHD, anxiety, bipolar disorder, and subjective well-being.

Predictor	Variance explained (%)
Neuroticism PGS	2.7
Schizophrenia PGS	2.0
P-factor PGS	1.8
Depression PGS	2.1
ADHD PGS	1.4
Anxiety PGS	1.5
Bipolar disorder PGS	1.6
Subjective well-being PGS	1.6
Height PGS	1.5
Multivariate PGS model	3.0
Family history	4.4

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