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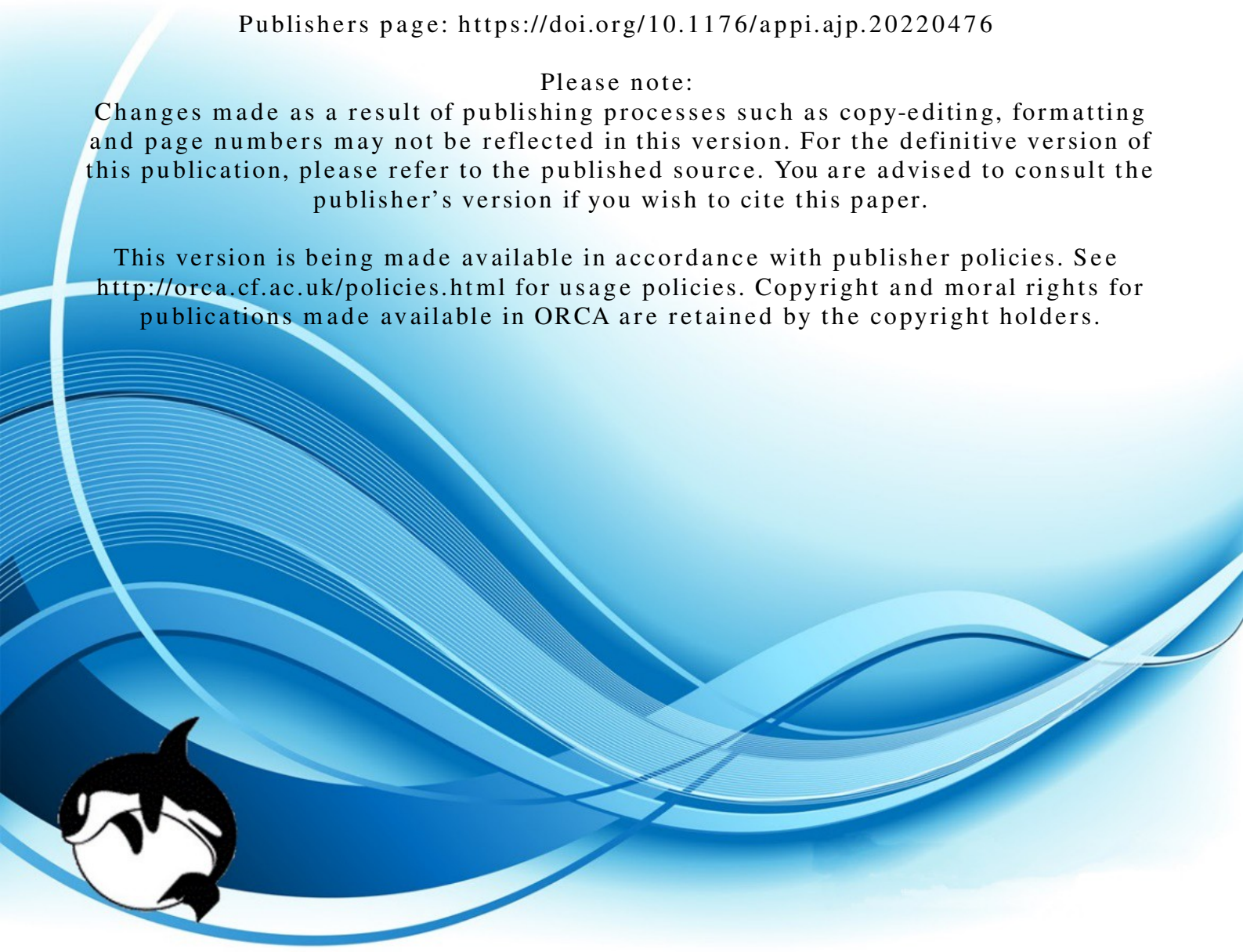

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Polygenic scores and onset of major mood or psychotic disorders among offspring of affected parents

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Disclosures

Dr. Nurnberger is an investigator for Janssen, with interests unrelated to the current work. Dr. McInnis has consulted with Janssen and Otsuka Pharmaceuticals and has received research support from Janssen. None of the remaining authors have any potential conflicts of interest to disclose.

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Abstract

Objective: Family history is an established risk factor for mental illness. We sought to investigate whether polygenic scores (PGS) can complement family history to improve identification of risk for major mood and psychotic disorders.

Methods: We combined 8 cohorts to create a sample of 1884 participants aged 2-36 years, including 1339 offspring of parents with mood or psychotic disorders, who were prospectively assessed over an average of 5.1 years using diagnostic interviews. We constructed PGS for depression, bipolar disorder, anxiety, attention-deficit/hyperactivity disorder (ADHD), schizophrenia, neuroticism, subjective well-being, p-factor, and height (negative control). We used Cox regression to test associations between PGS, family history of major mental illness, and onsets of major mood and psychotic disorders.

Results: There were 435 onsets of major mood and psychotic disorders across follow-up. PGS for neuroticism (HR 1.23, 95%CI 1.12-1.36), schizophrenia (HR 1.15, 95%CI 1.04-1.26), depression (HR 1.11, 95%CI 1.01-1.22), ADHD (HR 1.10, 95%CI 1.00-1.21), subjective well-being (HR 0.90, 95%CI 0.82-0.99), and p-factor (HR 1.14, 95%CI 1.04-1.26) were associated with onsets. After controlling for family history, neuroticism PGS remained significantly positively associated (HR 1.19, 95%CI 1.08-1.31) and subjective well-being PGS remained significantly negatively associated (HR = 0.89, 95%CI 0.81 to 0.98) with onsets.

Conclusions: Neuroticism and subjective well-being PGS capture risk of major mood and psychotic disorders that is independent of family history, whereas PGS for psychiatric illness provide limited predictive power when family history is known. Neuroticism and subjective well-being PGS may complement family history in the early identification of those at elevated risk.

Introduction

Major mood and psychotic disorders, including major depressive disorder, bipolar disorder, and schizophrenia spectrum disorder, have a pervasive impact on health (1). As a result, there have been calls to prioritize early identification and prevention of these disorders (2). The best available predictor of major mental illness is having a biological relative who is affected (3). However, family history information is not sufficient to accurately identify *which* individuals are most likely to become ill. This is partly because most people with a positive family history will not be affected (4). Additionally, family history may not be known in full due to stigma associated with mental illness and the demographic trend toward smaller families limits our ability to obtain a complete picture of family history. It has been shown that genetic and environmental risk factors for major mental disorders are largely shared across diagnostic categories (5). Therefore, it is desirable to identify early, stable predictors of illness across diagnostic categories. In the present study, we sought to test whether polygenic scores improved identification of risk for mood and psychotic disorders over family history information alone.

Polygenic scores (PGS) can be used to summarize genetic predisposition to a disease or trait based on common variants across the genome (6). PGS are calculated by summing associated alleles from a discovery genome-wide association study (GWAS) weighted by their effect sizes (7). Using this method, we can calculate PGS indexing genetic liability to a range of phenotypes. It is also possible to combine genetic predisposition to multiple forms of psychopathology into a single score indexing general genetic liability to psychopathology (a 'p-factor score') (8). The utility of PGS in prospectively identifying risk of major mood and psychotic disorders among youth with a family history of these disorders has not yet been examined.

There is a clear relationship between PGS for psychiatric disorders and psychopathology among youth (9–11). Among individuals from families densely affected by mental illness, higher PGS for schizophrenia and bipolar disorder are associated with the presence of these disorders (12). PGS for schizophrenia have been shown to improve the prediction of psychosis among adults in a clinical high-risk sample (13). However, it is not known whether PGS can meaningfully complement family history of major mood and psychotic disorders to identify risk of these disorders.

In the present study, we examined the relationship between PGS, family history of major mood and psychotic disorders, and onset of these disorders in young people. We defined family history of mental illness as the presence of a major mood or psychotic disorder in a biological parent. We selected PGS for major depressive disorder (14), bipolar disorder (15), schizophrenia (16), anxiety disorders (17), attention-deficit/hyperactivity disorder (ADHD) (18) and constructed a p-factor PGS that encompassed combined genetic liability to these disorders (19). We included PGS for neuroticism and subjective well-being, because these dimensional phenotypes have been associated with multiple forms of mental illness (20,21). We hypothesized that PGS would improve prediction of major mood and psychotic disorders over family history information alone. We tested this hypothesis in a unique sample enriched for familial risk of mood and psychotic disorders, that is composed of 8 cohorts from 6 countries.

Methods

Sample description

Participants ranged in age from 2-31 years (mean 13.66, SD 5.37) at first assessment and were enrolled in one of 8 longitudinal cohorts: (1) the Families Overcoming Risks and Building Opportunities for Well-being (FORBOW) study (22), (2) the Maritime Bipolar Family Study (MBFS) (23), (3) the USA Bipolar High-Risk Project (USAB) (24), (4) the Pittsburgh Bipolar Offspring Study (BIOS) (25), (5) the Early Prediction of Adolescent Depression study (EPAD) (26), (6) the Bipolar and Schizophrenia Young Offspring Study (BASYS) (27), (7) the Dutch Bipolar and Schizophrenia Offspring Study (DBSOS) (28), and (8) the Sydney Bipolar Kids and Sibs study (29). The sample included offspring of parents with major mood or psychotic disorders, defined as bipolar disorder, recurrent/chronic major depressive disorder, or schizophrenia spectrum disorder, in addition to offspring of control parents. Offspring of affected parents were recruited through mental health services. Offspring of control parents were recruited through advertisements and community organizations. Participants were assessed at regular intervals and the median follow-up duration was 3 years (range 0-18 years). Study protocols were approved by each cohort's local institutional Research Ethics Board and all participants, or their parents/guardians, provided informed consent.

Assessment of family history

The parents of participants were assessed for mental disorders using semi-structured diagnostic interviews. Offspring of parents with bipolar disorder, recurrent/chronic major depressive disorder, or schizophrenia spectrum disorder were considered to have a positive family history of

major mood or psychotic disorders. Additional information outlining assessment of parent psychopathology is provided in Supplemental Methods.

Assessment of psychopathology

Participants were assessed for mental disorders at regular intervals using diagnostic interviews (30–32). Assessors were blind to parent psychopathology or to the specific hypotheses of the study. Diagnoses were confirmed in consensus meetings with clinicians who were blind to parent psychopathology. We defined an onset of major mood or psychotic disorder as a prospectively assessed diagnosis of major depressive disorder, bipolar disorder, or schizophrenia spectrum disorder. Additional cohort-specific information outlining recruitment and assessment of psychopathology is provided in Supplemental Methods.

Polygenic scores

Genotyping was carried out separately for each cohort. Genetic quality control was performed following the same procedure for each cohort (Supplemental Methods). Genetic data from all cohorts were merged post-imputation. We excluded individuals with self-reported non-European ancestry. PGS were constructed with PRSice-2 (7), using GWAS summary statistics for major depressive disorder (14), bipolar disorder (15), schizophrenia (16), anxiety disorders (17), ADHD (18), subjective well-being (21), and neuroticism (20). As a negative control, we also calculated a PGS for height (33), a trait with a large genetic contribution, to establish specificity of the effects. We pruned genotypes using clumping to obtain an independent set of SNPs in approximate linkage equilibrium with an $r^2<0.1$ within any 500 kb window. We weighted the contribution of each allele by the effect size of its association with each phenotype in the discovery GWAS. To avoid overlap

between discovery and target samples, we used summary statistics omitting cohorts that had potential overlap with the target sample. Additionally, to construct a general psychopathology (p-factor) PGS, we first used genomic structural equation modelling (19) to conduct multivariate GWAS using univariate summary statistics from GWAS of major depressive disorder, bipolar disorder, schizophrenia, anxiety disorders, and ADHD. Next, we used summary statistics from the resulting multivariate GWAS to calculate the p-factor PGS. To minimize the number of tests conducted, we used PGS at p-value thresholds that maximally capture the phenotypic variance in the discovery GWAS samples in analyses: 0.001 for height (33), 0.05 for major depressive disorder and schizophrenia (14,16), 0.10 for bipolar disorder (15), 0.50 for ADHD and neuroticism (18,20), and 1.00 for anxiety (17), subjective well-being (21), and p-factor (19). The independent discovery GWAS sample size for each phenotype and the number of SNPs included in each PGS are shown in Supplemental Table 1 and 2.

Statistical analyses

We tested the associations between PGS, family history of major mood and psychotic disorders, and onset of any of these disorders using Cox proportional hazards regression (coxme package (34)) and Kaplan-Meier estimation (survminer (35) and survival (36) packages). We used chronological age as survival time in all models. We accounted for the non-independence of observations from related individuals by including the family identifier as a random effect in Cox proportional hazards models. We verified the proportional hazards assumption using the Schoenfeld residuals test (Supplemental Results and Supplemental Figure 6). Diagnostic information from all follow-ups was included in analyses. We first tested the effect of each PGS on onsets of major mood and psychotic disorders. We estimated the proportion of variance in time

until diagnosis of major mood or psychotic disorder explained by the fixed effects in each model using likelihood-ratio based pseudo R^2 (Supplemental Table 4). Next, we tested the independent effect of each PGS on onsets of mood and psychotic disorders when accounting for familial high-risk status as a dichotomous variable. We then tested interactions between PGS and family history where an independent effect of PGS was observed. In addition to survival time, all models accounted for sex, follow-up duration, and genetic population structure indexed with 10 genetic principal components. To ensure that results were consistent across cohorts and not driven by a subset of participants, we tested the robustness of the main findings using cohort-wise leave-one-out analyses. Associations were quantified as hazard ratios. All PGS were standardized so that hazard ratios represent the effect of an increase of 1 standard deviation in the PGS. Analyses were implemented in RStudio (R version 4.0.1).

Results

Demographic and clinical characteristics

Following genetic quality control, the final sample included 1884 participants from 925 families, aged 6-36 years at most recent follow-up. Table 1 presents the characteristics of the participants. The age distribution at most recent assessment across cohorts is shown in Figure 1. Nearly three-quarters (N = 1339, 71.1%) of participants had a biological parent with a major mood or psychotic disorder. Of the participants, 435 developed major depressive disorder, bipolar disorder, or psychotic disorder by the end of follow-up. As expected, family history of major mood and psychotic disorders was strongly, positively associated with risk of onset of these disorders (Hazard Ratio (HR) 2.82, 95% CI 2.15 to 3.70, p <0.001; Supplemental Figure 1). We also found the expected relationships between PGS and family history of major mood or psychotic disorders; higher PGS for bipolar disorder, p-factor, neuroticism, major depression, schizophrenia, ADHD, and anxiety were significantly positively associated with family history of illness (Supplemental Figure 2). The relationships between PGS are shown in Supplemental Figure 3.

The relationship between polygenic scores and onsets of major mental disorders

Higher polygenic scores for multiple phenotypes were associated with onset of mood and psychotic disorders (Figure 2). After accounting for age, follow-up duration, sex and genetic principal components, PGS for neuroticism (HR 1.23, 95% CI 1.12 to 1.36, p < 0.001), schizophrenia (HR 1.15, 95% CI 1.04 to 1.26, p = 0.007), depression (HR 1.11, 95% CI 1.01 to 1.22, p = 0.038), ADHD (HR 1.10, 95% CI 1.00 to 1.21, p = 0.044), and p-factor (HR 1.14, 95% CI 1.04 to 1.26, p = 0.006) were positively associated with onset of major mood and psychotic disorders. PGS for subjective well-being was negatively associated with illness onset (HR 0.90,

95% CI 0.82 to 0.99, p = 0.040). As expected, height PGS was not associated with disorder onset (HR 0.96, 95% CI 0.87 to 1.06, p = 0.470). This pattern of associations was confirmed, with all effect sizes within 1 standard error of the original finding, in sensitivity analyses restricted to individuals followed up until age 15 years or older and adjusting for study (Supplemental Results).

The unique contribution of polygenic scores to onsets of major mental illness

PGS for neuroticism and subjective well-being were significantly associated with onsets of major mood and psychotic disorders, independent of family history of these disorders (Figure 2). After accounting for family history, neuroticism PGS remained positively associated with onsets of major mood and psychotic disorders (HR 1.19, 95% CI 1.08 to 1.31, $p < 0.001$) and subjective well-being PGS remained negatively associated with onsets of these disorders (HR 0.89, 95% CI 0.81 to 0.98, p = 0.017). The independent effect of neuroticism PGS was consistent across all cohort-wise leave-one-out analyses (HR range 1.16-1.22; Supplemental Figure 4). The independent effect of the subjective well-being PGS was directionally consistent across cohorts (HR range 0.82-0.92) and was statistically significant on 6 of the 8 cohort-wise leave-one-out analyses (Supplemental Figure 5).The effect of neuroticism PGS on disorder onset was stronger in the absence of family history of mood and psychotic disorders, reflected in a statistically significant interaction between family high-risk status and neuroticism PGS (HR 0.75, 95% CI 0.58 to 0.98, p = 0.035). Offspring of controls with low neuroticism PGS had the lowest probability of diagnosis, followed by offspring of controls with high neuroticism PGS, then offspring of affected parents with low neuroticism PGS, and finally offspring of affected parents with high neuroticism PGS had the highest probability of diagnosis (Kaplan-Meier $\chi^2 = 39.40$, $p < 0.001$; Figure 3). There was no interaction between subjective well-being PGS and family history of major

mood and psychotic disorders (HR = 1.09, 95% CI 0.85 to 1.41, p = 0.480). This pattern of associations was confirmed, with all effect sizes within 1 standard error of the original finding, in sensitivity analyses restricted to individuals followed up until age 15 years or older and adjusting for study (Supplemental Results).

Discussion

This study identified associations between polygenic scores, family history of major mood and psychotic disorders, and onset of these disorders in youth. We found that polygenic scores for neuroticism and subjective well-being uniquely contributed to identification of risk of major mental illness, over and above the well-established effect of family history. In contrast, individuals with higher genetic predisposition to schizophrenia, major depressive disorder, ADHD and a genetic 'p-factor' were, as expected, more likely to develop major mood or psychotic disorders, but these polygenic scores did not improve identification of risk beyond family history alone. These findings suggest that PGS have the potential to improve risk identification in cases where family history information is not available or not known in full.

This study was motivated by a need to improve identification of risk for major mental disorders. It has been shown that PGS derived from GWAS of adult psychiatric phenotypes are associated with psychopathology earlier in life (11). We confirmed that genetic liabilities to neuroticism, depression, and subjective well-being indexed from GWAS of adult participants are associated with psychopathology among youth. Our results also aligned with those from past studies showing that offspring of parents with mood and psychotic disorders and individuals with these disorders have elevated PGS for psychopathology compared to controls (10,12). Our findings expand on these studies to show that PGS have the potential to improve upon current strategies for identification of risk for major mental disorders. While PGS for several disorders were associated with onset of mood or psychotic disorders, their effects largely overlapped with the known effect of family history. These findings suggest that PGS for psychiatric illness may provide limited predictive power when family history information is available. In contrast, the effects of

neuroticism and subjective well-being PGS were unique and independent of family history. This may be due in part to the transdiagnostic nature of these phenotypes. Transdiagnostic indicators of risk may be particularly valuable in the developmental context, where early manifestations of psychopathology typically begin in childhood or adolescence but often change in form over time. Neuroticism and subjective well-being PGS may capture some of this higher-level transdiagnostic liability to major mood and psychotic disorders that is independent of family history. The effect of neuroticism PGS on disorder onset was stronger in the absence of family history of mood and psychotic disorders. Thus, neuroticism PGS may help stratify degrees of risk, especially among offspring of unaffected parents. To our knowledge, this is the first time that an interaction between family history and a polygenic score has been reported in a prospective study of risk for mental disorders, and the replicability of this result should be tested in independent samples. Interestingly, the association between subjective well-being PGS and onset of major mood and psychotic disorders strengthened when we accounted for family history of these disorders. This suggests that the subjective well-being PGS may be useful in identifying individuals at higher risk of major mood and psychotic disorders, particularly those with a positive family history of these disorders.

Our findings have implications for future research. The finding that genetic liability to neuroticism is associated with increased risk of major mood and psychotic disorders independent of family history suggests that neuroticism PGS may be a useful tool for improved risk identification in early intervention studies. While the effects of PGS on psychopathology are modest, clinical implementation of PGS may be most useful in populations with a higher prior probability of disease, such as among offspring of affected parents (6). Approximately 1 out of every 3 offspring of a parent with a mood or psychotic disorder will become ill by adulthood (3). However, family

history information is inherently limited (4) and is often not known in full, so it is necessary to identify additional predictive factors. Genetic factors are set from conception and thus provide a stable tool that could be used in conjunction with other factors such as family history information, and more dynamic risk factors such as environmental exposures or clinical features, to allow for early identification of individuals at the highest risk. It has been suggested that earlier interventions produce the greatest benefit (37). The identification of stable, transdiagnostic indicators of risk opens the door for targeted, early interventions that may eventually reduce the individual and societal burden of these disorders.

Our study benefits from the inclusion of offspring of parents with major mood and psychotic disorders. Over 70% of the participants in our study have a biological parent with major depressive disorder, bipolar disorder, or a schizophrenia spectrum disorder, resulting in a concentration of familial risk and thus a higher rate of psychopathology than in the general population. We also benefit from 8 longitudinal cohorts, each with thorough diagnostic assessments repeated over multiple follow-up years and across ages with high retention rates. This allowed us to follow participants through the period of highest risk of major mental illness onset and examine the association between PGS and psychopathology over time. However, the results should be interpreted in the context of the study's limitations. One limitation is the heterogeneity of parent diagnoses across cohorts. We opted to include all available cohorts and to select a transdiagnostic outcome (onset of any major mood or psychotic disorder) because it has been shown that familial transmission of major mental illness is largely transdiagnostic (3,5). We have performed leave-one-out analyses to probe the robustness to cohort effects and confirm that the main findings are not driven by any single cohort. Our study is also limited by the binary definition of family history.

More nuanced family history information may be more predictive, but this information was not consistently collected across all contributing samples. Even with the combined sample, our study is also limited by statistical power. The limited statistical power increases the likelihood of false-negative results, particularly if a true weak relationship exists between predictor and outcome. This may be the case for PGS that were not significantly associated with illness onset when accounting for family history. Thus, these results await confirmation in larger studies. Another important limitation is the ethnically homogenous nature of the sample. We included only individuals of European descent, because current PGS methods rely on having matched genetic ancestry between the target sample and the GWAS from which reference effect sizes were derived. Currently, most large-scale GWAS are based on white individuals of European ancestry. As PGS move from the research setting to the clinic, this limitation may lead to exacerbation of the systemic health disadvantages already experienced by racially marginalized populations (38). It is our hope that our analyses will be extended to more inclusive samples as large-scale GWAS of racially diverse populations become available.

In conclusion, we found that genetic predisposition to neuroticism and subjective well-being uniquely contribute to risk of major mood and psychotic disorders beyond the effect of family history of these disorders. Future studies could probe the ability of neuroticism and subjective well-being PGS to predict onsets of major mood and psychotic disorders in diverse independent samples. The results may inform targeted early interventions to prevent onset of major mood and psychotic disorders among high-risk children and adolescents.

Table 1. Demographic and clinical characteristics of the study population, stratified by cohort.

	Cohort															
	BASYS (N = 96)		**FORBOW (N = 325)**		**EPAD (N = 285)**		**USAB (N = 274)**		**DBSOS (N = 97)**		**BK&S (N = 229)**		**BIOS (N = 414)**		**MBFS (N = 164)**	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age at first assessment (years)	11.1	3.4	10.8	4.0	12.2	2.1	15.6	3.2	13.2	2.3	20.2	5.2	10.3	4.7	19.7	4.1
Age at last assessment (years)	14.1	3.5	15.1	4.2	14.6	2.1	17.7	3.2	17.2	2.6	22.3	5.2	22.9	5.9	23.1	4.4
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Females	51	53.1	173	53.2	168	58.9	133	48.5	49	50.5	119	52.0	215	51.9	96	58.5
Parent diagnosis																
Major depression	0	0	143	44.0	285	100	0	0	0	0	0	0	0	0	21	12.8
Bipolar disorder	28	29.1	66	20.3	0	0	198	72.3	49	50.5	145	63.3	256	61.8	73	44.5
Psychotic disorder	16	16.7	23	7.1	0	0	0	0	20	20.6	0	0	0	0	0	0
Controls	52	54.2	93	28.6	0	0	76	27.7	28	28.9	84	36.3	158	38.2	70	42.7
Offspring diagnosis																
Major depression	5	5.2	56	17.2	29	10.2	40	14.6	16	16.5	51	22.3	139	33.6	30	18.3
Bipolar disorder	0	0	7	2.2	4	1.4	26	9.5	6	6.2	2	0.9	28	6.8	26	15.9
Psychotic disorder	0	0	7	2.2	0	0	1	0.4	0	0	0	0	4	1.0	3	1.8

Cohort abbreviations: BASYS = Bipolar and Schizophrenia Young Offspring Study (27); FORBOW = Families Overcoming Risks and Building Opportunities for Well-being study (22); EPAD = Early Prediction of Adolescent Depression study (39); USAB = USA Bipolar High-Risk Project (24); DBSOS = Dutch Bipolar and Schizophrenia Offspring Study (40); BK&S = Sydney Bipolar Kids and Sibs study (29); BIOS = Pittsburgh Bipolar Offspring Study (25); MBFS = Maritime Bipolar Family Study (23).

Figure 1. Age at most recent assessment, stratified by cohort.

BASYS = Bipolar and Schizophrenia Young Offspring Study (27); FORBOW = Families Overcoming Risks and Building Opportunities for Well-being study (22); EPAD = Early Prediction of Adolescent Depression study (39); USAB = USA Bipolar High-Risk Project (24); DBSOS = Dutch Bipolar and Schizophrenia Offspring Study (40); BK&S = Sydney Bipolar Kids and Sibs study (29); BIOS = Pittsburgh Bipolar Offspring Study (25); MBFS = Maritime Bipolar Family Study (23).

Figure 2. Relationships between polygenic scores and onsets of major mood and psychotic disorders.

HR = Hazard ratio; Bars represent confidence intervals corresponding to $\alpha = 0.05$.

Figure 3. Kaplan-Meier plot showing the relationship between neuroticism PGS, family history of major mood and psychotic disorders and onsets of these disorders, with the sample divided into terciles based on PGS. Curves shown are: (1) no family history of major mental illness and bottom neuroticism PGS tercile (Control/Bottom), (2) no family history of major mental illness and top neuroticism PGS tercile (Control/Top), (3) family history of major mental illness and bottom neuroticism PGS tercile (FHR/Bottom), and (4) family history of major mental illness and top neuroticism PGS tercile (FHR/Top).

Number at risk					
	0 years	**5 years**	**10 years**	**15 years**	**20 years**
Control/Bottom	158	156	151	95	16
Control/Top	111	108	104	59	16
FHR/Bottom	333	320	301	183	30
FHR/Top	417	403	379	215	28

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