Polygenic Risk and Progression to Bipolar or Psychotic Disorders Among Individuals Diagnosed With Unipolar Depression in Early Life

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Objective: The authors investigated the associations between polygenic liability and progression to bipolar disorder or psychotic disorders among individuals diagnosed with unipolar depression in early life.

Methods: A cohort comprising 16,949 individuals (69% female, 10–35 years old at the first depression diagnosis) from the iPSYCH Danish case-cohort study (iPSYCH2012) who were diagnosed with depression in Danish psychiatric hospitals from 1994 to 2016 was examined. Polygenic risk scores (PRSs) for major depression, bipolar disorder, and schizophrenia were generated using the most recent results from the Psychiatric Genomics Consortium. Hazard ratios for each disorder-specific PRS were estimated using Cox regressions with adjustment for the other two PRSs. Absolute risk of progression was estimated using the cumulative hazard.

Results: Patients were followed for up to 21 years (median=7 years, interquartile range, 5–10 years). The absolute risks of progression to bipolar disorder and psychotic disorders were 7.3% and 13.8%, respectively. After mutual adjustment for the other PRSs, only the PRS for bipolar disorder predicted progression to bipolar disorder (adjusted hazard ratio for a one-standard-deviation increase in PRS=1.11, 95% CI=1.03, 1.21), and only the PRS for schizophrenia predicted progression to psychotic disorders (adjusted hazard ratio=1.10, 95% CI=1.04, 1.16). After adjusting for PRSs, parental history still strongly predicted progression to bipolar disorder (adjusted hazard ratio=5.02, 95% CI=3.53, 7.14) and psychotic disorders (adjusted hazard ratio=1.63, 95% CI=1.30, 2.06).

Conclusions: PRSs for bipolar disorder and schizophrenia are associated with risk for progression to bipolar disorder or psychotic disorders, respectively, among individuals diagnosed with depression; however, the effects are small compared with parental history, particularly for bipolar disorder.

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Individuals with bipolar disorder or psychotic disorders frequently experience depression before their first bipolar disorder or psychotic diagnosis (1–6). In many instances, depression is what brings these individuals into contact with the mental health care system, months or even years before the onset of their first manic or psychotic symptoms (7–9). This point of contact represents an opportunity for early identification and intervention. Identification and intervention at this stage may improve patient outcomes by enabling informed decisions regarding medication management and decreasing the duration of untreated psychosis (10, 11). However, depression is common, and the majority of patients with depression do not go on to develop bipolar or psychotic disorders (12, 13). Information that can help identify patients with depression who will later progress to bipolar disorder or a psychotic disorder would be of great utility for both psychiatrists and their patients.

A substantial proportion of the population-level variance in bipolar disorder and psychotic disorders, particularly schizophrenia, is attributable to genetic factors (14–16). Previous research has demonstrated overlap among the genetic architectures of depression, bipolar disorder, and schizophrenia (17–20); however, a portion of risk variants may be disorder specific (21). This raises the possibility that measures of genetic liability could be used to identify patients with depression who are likely to develop bipolar disorder or psychotic disorders and possibly even differentiate between those who are at increased risk for one disorder type over the other. Additionally, studies

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of clinical predictors of progression to bipolar disorder or schizophrenia have consistently found that parental history is either the strongest predictor or one of the strongest predictors of progression (12, 13, 22), which supports the hypothesis that risk for progression is determined partly by genetic factors. Interestingly, previous studies conducted by our group found that the effect of parental history also appeared to be disorder specific, such that a parental history of bipolar disorder in individuals with depression predicted progression to bipolar disorder but not schizophrenia, while a parental history of schizophrenia predicted progression to schizophrenia but not bipolar disorder (12, 13). However, although parental history is often used as a marker of genetic liability, there are alternative mechanisms through which mental illness in a parent can affect the onset or course of mental illness in offspring. For example, a person with a parent with bipolar disorder may be more likely to recognize symptoms in him- or herself and seek treatment (23), or this parental history could influence diagnostic decisions made by a treating psychiatrist. To test this hypothesis, it is therefore necessary to measure genetic liability directly.

Our primary goal in this study was to evaluate the extent to which genetic liability, measured directly using polygenic risk scores (PRSs), is associated with progression to bipolar disorder or psychotic disorders among individuals diagnosed with unipolar depression. To accomplish this, we generated PRSs quantifying genetic liability to major depression, bipolar disorder, and schizophrenia and tested whether these scores were associated with progression to bipolar disorder or psychotic disorders in a representative sample of patients diagnosed with unipolar depression in Danish psychiatric hospitals. As a secondary goal, we aimed to assess the potential utility of PRS as a marker of progression risk in clinical settings by examining the absolute risk of progression among individuals with different levels of genetic liability and comparing this to the absolute risk associated with having a parental history of bipolar disorder or psychotic disorders.

METHODS

Data Sources

Data were obtained from the iPSYCH Danish case-cohort study (iPSYCH2012). This sample includes all individuals born in Denmark between 1981 and 2005 who received a diagnosis of affective disorder, schizophrenia, autism, attention deficit hyperactivity disorder (ADHD), or anorexia nervosa in a publicly funded psychiatric hospital through December 31, 2012, as well as a random sample of 30,000 individuals drawn from the Danish population born between 1981 and 2005 who survived to their first birthday and had known mothers (24). Cases were identified from the Danish Psychiatric Central Research Register (DPCRR) (25), which includes all psychiatric diagnoses given in inpatient settings at Danish psychiatric hospitals from 1969 to 1994, as well as diagnoses given in inpatient, outpatient, and emergency department settings from 1995 onward. Diagnoses in the DPCRR are assigned at discharge by a treating psychiatrist on the basis of ICD-8 criteria from 1969 to 1993 and ICD-10 criteria from 1994 onward (26). Cases in the iPSYCH2012 sample were selected from a version of the DPCRR that was complete through 2012 (24); however, information on diagnoses through 2016 is now available through a register update.

This study was approved by the Danish Data Protection Agency and the Danish Health Data Authority. We did not obtain informed consent from participants, because it is not required for register-based studies, in accordance with Danish law.

Genotyping

Genotyping of members of the iPSYCH2012 case-cohort sample was done from blood spots collected at birth as part of routine clinical practice and stored in the Danish Newborn Screening Biobank (27). Blood spots were located for 93.3% of the original sample (N=80,422), and 90% of the original sample passed quality-control measures (N=77,639) (24). Genetic data for members of the iPSYCH2012 sample can be linked with information stored in Danish national registers, including the DPCRR, using the unique personal identification number assigned to all individuals born or residing legally in Denmark (28).

Study Sample

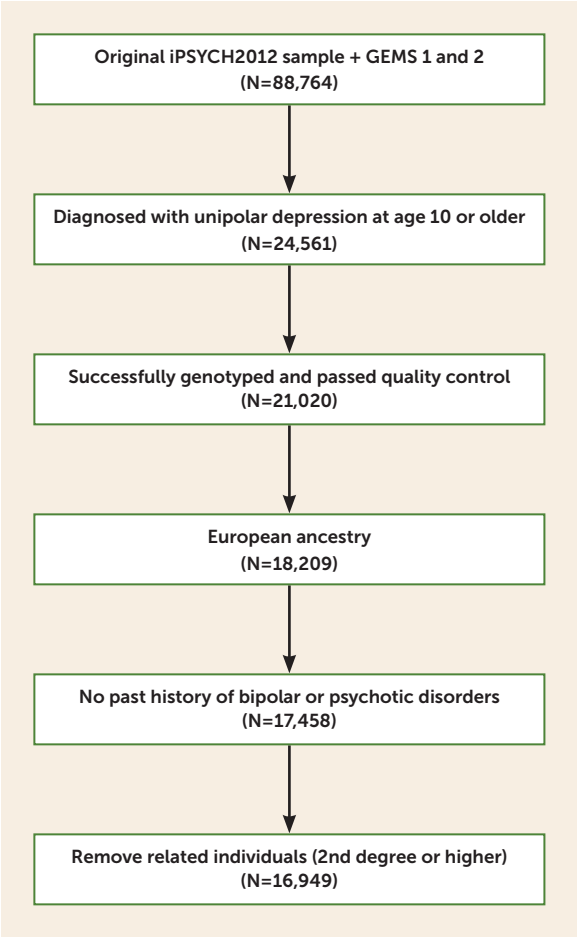
A flowchart of the sample selection process is presented in Figure 1. We defined a cohort of all individuals from the iPSYCH2012 sample who had received a primary, secondary, or underlying-cause diagnosis of depression (ICD-10 codes F32–F33) in a Danish psychiatric hospital at age ≥10; who were successfully genotyped and passed quality-control measures; who were of European ancestry as determined by principal component analysis; and who had no prior diagnoses of bipolar disorder (codes F30–F31) or psychotic disorders (codes F20–F29, excluding code F24) in the DPCRR. Finally, we removed at random one member from each pair of related individuals (pi-hat score >0.20 or second-degree relatedness or closer). The final study sample comprised 16,949 individuals.

To ensure that our study sample was representative of individuals treated for depression in hospital-based settings in Denmark, only individuals who were selected for inclusion in the iPSYCH2012 cohort on the basis of a depression diagnosis were included. Individuals selected for inclusion in iPSYCH2012 on the basis of a different psychiatric diagnosis (e.g., ADHD) who received a depression diagnosis after 2012 were not included. However, members of the iPSYCH2012 subcohort (i.e., the 30,000 individuals randomly selected from the Danish population regardless of case status) were included in our study sample regardless of when they received their depression diagnosis.

Measures

The main outcomes were a diagnosis of bipolar disorder (ICD-10 codes F30 and F31) or psychotic disorders (codes F20–F29, excluding code F24). As secondary outcomes, we

FIGURE 1. Flowchart of the selection process for the study sample[a]



[a] The GEnetiske og Miljømæssige årsager til Skizofreni (GEMS) samples are Danish case control genome-wide association studies of schizophrenia (ICD-10 code F20). The first GEMS sample (GEMS 1) includes 894 cases and 884 controls, and the second GEMS sample (GEMS 2) includes 995 cases and 980 controls. Cases from the GEMS samples were included among the iPSYCH Danish case-cohort study (iPSYCH2012), even though they were genotyped at an earlier date. Control subjects from the GEMS samples had the same probability of being selected for the subcohort as all other individuals from the base population.

examined conversion to schizophrenia (code F20) and psychotic depression (codes F32.3 and F33.3), as well as two composite categories: any affective psychotic disorder, which included both psychotic depression (codes F32.3 and F33.3) and psychotic bipolar disorder (codes F30.2, F31.2, and F31.5), and any disorder with psychotic features, a composite of all outcomes with psychotic features. For the analyses of progression to affective psychotic disorders, we removed individuals with psychotic depression as their first depression diagnosis (N=458). A list of specific ICD-10 codes included in each outcome category is presented in Table S1 in the online supplement.

The main exposures were PRS for major depression, PRS for bipolar disorder, and PRS for schizophrenia. PRSs were created using the LDpred method (infinitesimal model) (29) based on the most recent summary statistics from the Psychiatric Genomics Consortium and 23andMe (not including the iPSYCH2012 sample) (19, 30, 31). PRSs were standardized according to their means and standard deviations in the study population. Additionally, we examined the effects of parental history of bipolar disorder (ICD-8 codes 296.19, 296.39, and 298.19; ICD-10 codes F30 and F31) and psychotic disorders (ICD-8 codes 295.x, 297.x, 296.89, 298.29, 298.39, 298.89, 298.99, 299.04, 299.05, 299.09, and 301.83; ICD-10 codes F20–F29, excluding F24) and, for comparison, unipolar depression (ICD-8 codes 296.09, 296.29, 298.09, and 300.49; ICD-10 codes F32 and F33). Parental history was assessed by linking maternal and paternal personal identification numbers to the DPCRR. A proband was considered to have a parental history of one of these disorders if either the mother or the father received the diagnosis in a psychiatric hospital on or before the date of the proband's first depression diagnosis. Parental history was defined as a mutually exclusive, hierarchical variable such that parents were categorized according to the most severe diagnosis they received before the date of the proband's first depression diagnosis (that is, psychotic disorders took precedence over bipolar disorder, which took precedence over unipolar depression).

Analysis

Hazard ratios for the association between the PRSs for bipolar disorder, schizophrenia, and major depression and progression to bipolar disorder or psychotic disorders were estimated using Cox proportional hazards models, with days since the first depression diagnosis as the time metric. Models were adjusted for sex and the first five principal components and stratified by genotype wave (24) to control for batch effects. Because genotype wave correlates strongly with birth year, this stratification also partially controls for potential cohort effects. In addition, because previous research has shown substantial overlap in the underlying genetic liabilities for bipolar disorder, schizophrenia, and depression (17, 32), we obtained jointly estimated hazard ratios by including all three scores in the same regression model. Finally, we tested for interaction between PRS variables by fitting models with cross-product interaction terms. Absolute risks were estimated using cumulative hazards obtained from Cox regression models. Statistical significance was assessed at a Bonferroni-corrected alpha of 0.017 to account for the fact that effects were tested for three PRS scores. Analyses were conducted in SAS, version 9.4.

Sensitivity Analysis

We conducted four separate sensitivity analyses to evaluate the extent to which our sampling choices affected the effects of PRS on progression to bipolar disorder or psychotic disorders. First, we examined progression among only those patients with inpatient or outpatient hospital contacts. Second, we examined progression among only those patients with depression as their main diagnosis. Third, we examined progression in the full sample of depressed patients including close relatives, and, finally, we examined progression in the

TABLE 1. Demographic and clinical characteristics of patients with unipolar depression in a study of progression to bipolar and psychotic disorders (N=16,949)

Characteristic	N	%
Sex		
Female	11,675	68.9
Male	5,274	31.1
Treatment setting		
Outpatient	10,390	61.3
Inpatient	2,495	14.7
Emergency department	4,064	24.0
ICD-10 diagnostic code		
F32	13,655	80.6
F33	3,294	19.4
Severity		
Mild	2,969	17.5
Moderate	7,484	44.2
Severe	1,584	9.3
Psychotic	441	2.6
Unspecified	4,471	26.4
Diagnosis type		
Main	14,167	83.6
Secondary	2,773	16.4
Underlying cause	9	0.1
Age at diagnosis (years)		
10–18	7,041	41.5
19–24	6,562	38.7
25–29	3,241	19.1
30–35	105	0.6
Parental history of mental disorders		
Unipolar depression	1,468	8.7
Bipolar disorder	191	1.1
Psychotic disorder	498	2.9

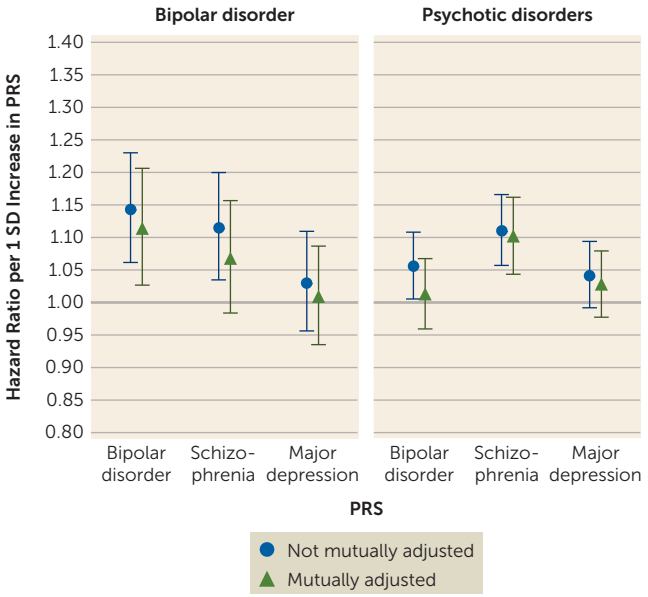
full sample including depressed patients of non-European genetic ancestry. We also ran models for each primary outcome with death as a competing event to ensure that our results were not biased by higher mortality rates among patients who would eventually progress to a diagnosis of bipolar disorder or psychotic disorders. Finally, some individuals (N=131) received diagnoses of both bipolar disorder and a psychotic disorder during follow-up assessment. These patients were treated as case subjects in the main analyses for both bipolar disorder and psychotic disorders; however, we verified whether the potential for multiple outcome states affected the PRS associations by fitting multistate models using the mstate package in R.

RESULTS

Sample Characteristics

The demographic and clinical characteristics of the study sample are summarized in Table 1. Patients were predominantly young (80% were diagnosed before age 25) and female (69%). The majority of patients (61%) were treated in outpatient settings, and the most common severity specification (44%) was moderate depression. More than

FIGURE 2. Associations between polygenic risk scores (PRSs) for bipolar disorder, schizophrenia, and major depression and hazard of progression to bipolar and psychotic disorders in individuals diagnosed with unipolar depression in Danish psychiatric hospitals[a]



[a] Mutually adjusted values indicate that the estimate was derived from a regression model containing all PRS variables as well as sex and the first five ancestral principal components.

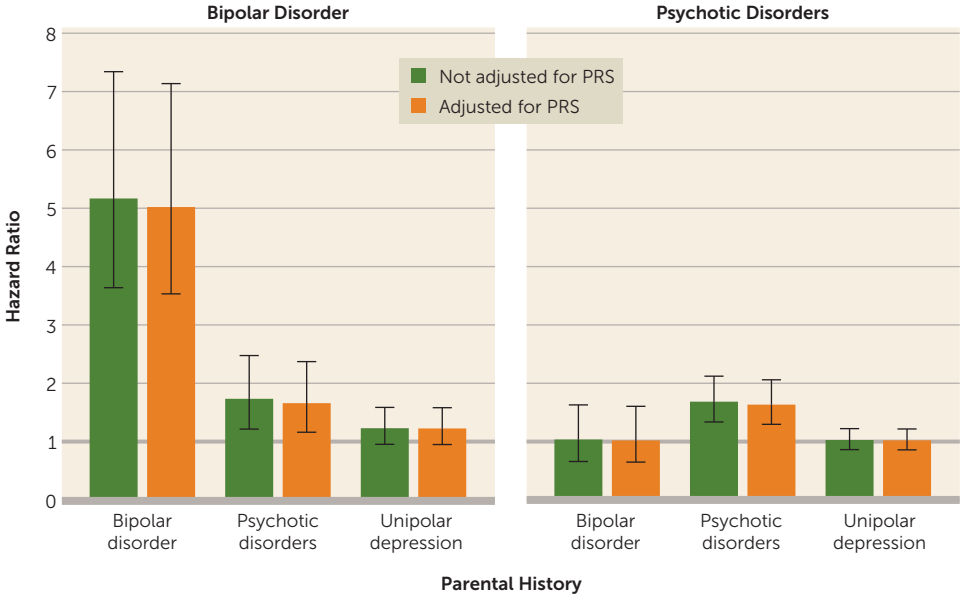
80% were diagnosed as having an ICD-10 code F32 single depressive episode, and 84% had depression as their main diagnosis. Participants were followed for a maximum of 21.1 years, with a median follow-up time of 7.3 years (interquartile range, 5.4–10.0 years) for bipolar disorder and 7.1 years (interquartile range, 5.1–9.8 years) for psychotic disorders.

The PRSs for bipolar disorder and schizophrenia were moderately correlated (Pearson's r=0.40, $p<0.0001$). There were weaker but significant correlations between the PRSs for major depression and for bipolar disorder (r=0.14, $p<0.0001$) and between the PRSs for major depression and for schizophrenia (r=0.13, $p<0.0001$). The mean PRSs among patients who progressed to bipolar disorder or psychotic disorders are listed in Table S2 in the online supplement, and hazard ratios are listed in Table S3.

Main Outcomes

PRSs for both bipolar disorder and schizophrenia were associated with progression to bipolar disorder in the unadjusted models; however, after mutual adjustment, only the PRS for bipolar disorder was significantly associated with progression to bipolar disorder (progression to bipolar disorder for each one-standard-deviation increase in PRS score for bipolar disorder, adjusted hazard ratio=1.11, 95% CI=1.03, 1.21, p=0.009). Only the PRS for schizophrenia was significantly associated with progression to psychotic disorders (adjusted hazard ratio=1.10, 95% CI=1.04, 1.16, p=0.0004) (Figure 2; see also Table S3 in the online supplement). There were no interactions between PRS variables.

FIGURE 3. Parental history and hazard of progression from depression to bipolar or psychotic disorders, adjusted and unadjusted for polygenic risk[a]



[a] All models were adjusted for sex. Models with polygenic risk score (PRS) variables were also adjusted for the first five ancestral principal components. PRS refers here to the PRS variable associated with the particular outcome (e.g., for the outcome of bipolar disorder, PRS represents the PRS for bipolar disorder).

Secondary Outcomes

The effect of the PRS for schizophrenia on the hazard of progression to schizophrenia was slightly smaller than its effect on progression to psychotic disorders more generally (adjusted hazard ratio=1.08, 95% CI=1.00, 1.17, p=0.05). The PRS for schizophrenia had the strongest association with progression to any disorder with psychotic features (adjusted hazard ratio=1.08, 95% CI=1.02, 1.14, p=0.005) (see Figure S1 in the online supplement), but this is relatively uninformative given that psychotic disorders constituted more than 80% of the diagnoses in this category (see Table S1 in the online supplement).

There was a statistically significant interaction (β=0.18, p<0.0001) between the PRSs for bipolar disorder and for schizophrenia as risk factors for progression to affective psychotic disorders (both as a composite category and for psychotic depression alone). Depressed patients with high PRSs for both bipolar disorder and schizophrenia were at increased risk for progression to affective psychosis; however, among patients with low liability for either bipolar disorder or schizophrenia, higher liability for the other was associated with decreased risk for affective psychotic disorders (see Figure S2 in the online supplement).

PRS and Parental History

The effects of parental history on progression to bipolar disorder and psychotic disorders are shown in Figure 3. There was a significant effect of parental history on the hazard of progression to psychotic disorders and, in particular, to bipolar disorder, such that patients with a parental history of bipolar disorder were more than five times as likely to progress to bipolar disorder compared with patients with no parental history, and patients with a parental history of psychotic disorders were 63% more likely to progress to psychotic disorders compared with individuals with no parental history. The mean PRSs for bipolar disorder and schizophrenia were higher among patients with a parental history of bipolar disorder and psychotic disorders, respectively, compared with individuals with no parental history (see Figure S3 in the online supplement). However, the associations between parental history and progression were only slightly attenuated after controlling for PRS variables (Figure 3). For progression to secondary outcomes, only parental history of psychotic disorders was associated with progression to schizophrenia or any psychotic diagnosis (see Figure S4 in the online supplement).

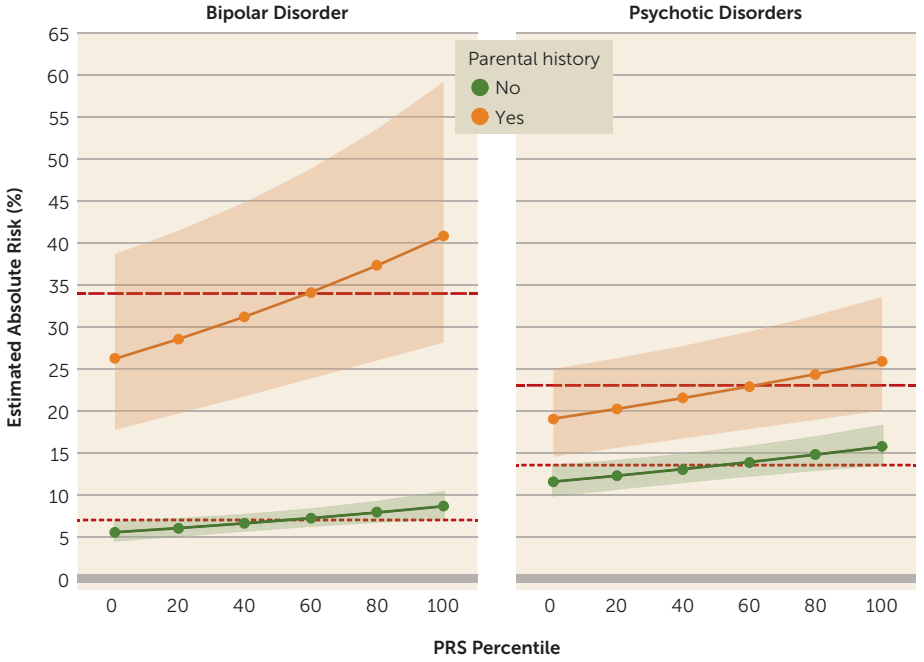
Absolute Risk of Progression by Parental History and Polygenic Liability

Overall, absolute risk of progression to bipolar disorder and psychotic disorders was 7.3% (95% CI=6.4, 8.3; N=712) and 13.8% (95% CI=12.2, 15.5; N=1,640), respectively (see Table S4 in the online supplement). The absolute risks of progression to bipolar disorder and psychotic disorders by PRS quartile are summarized in Table S5 in the online supplement. The estimated absolute risk of progression to bipolar disorder increased by approximately 0.5% per quartile of PRSs for bipolar disorder, and the estimated absolute risk of progression to psychotic disorders increased by approximately 1% per PRS quartile. In the top 1% of PRSs for bipolar disorder, absolute risk of progression to bipolar disorder was 9.1% (95% CI=7.6, 10.8) compared with 5.7% (95% CI=4.7, 6.9) in the bottom 1%. For PRSs for schizophrenia, absolute risk among the top 1% was 16.2% (95% CI=14.0, 18.7) compared with 11.6% (95% CI=10.0, 13.5) for the bottom 1%.

We estimated the absolute risk of progression to bipolar disorder and psychotic disorders separately among individuals with and without a parental history (Figure 4). Individuals who ranked in the top 1% of PRSs for bipolar disorder who also had a parental history of bipolar disorder had a 40.8% estimated absolute risk of progressing to bipolar disorder, compared with a 26.2% risk among individuals in the bottom quartile with a parental history of bipolar disorder and a 5.6% risk among individuals in the bottom quartile with

no parental history. Individuals who ranked in the top 1% of PRSs for schizophrenia who also had a parental history of psychotic disorders had a 25.9% absolute risk of converting to a psychotic disorder, compared with 19.1% among individuals in the bottom quartile with a parental history of psychotic disorders and an 11.6% risk among individuals in the bottom quartile with no parental history.

FIGURE 4. Absolute risk of progression to bipolar disorder or psychotic disorders among individuals diagnosed with unipolar depression in Danish psychiatric hospitals, stratified by polygenic risk and parental history[a]



[a] Parental history refers to parental history of the specific outcome (bipolar disorder or psychotic disorders), and polygenic risk score (PRS) refers to the PRS for the specific outcome (bipolar disorder or schizophrenia). Dashed horizontal lines represent the absolute risk of conversion based on parental history alone, irrespective of polygenic liability. Shaded bands represent 95% confidence intervals for the cumulative hazard estimates.

Sensitivity Analysis

The pattern of results for the primary outcomes was similar across all sensitivity analyses, suggesting that our results were fairly robust to sampling choices (see Tables S6–S9 in the online supplement). The same held true for the secondary outcomes, except that the effects of PRS for bipolar disorder on psychotic depression (adjusted hazard ratio=1.15, 95% CI=1.01, 1.31, p=0.04) and affective psychotic disorders (adjusted hazard ratio=1.21, 95% CI=1.07, 1.37, p=0.002) were stronger when only main diagnoses were considered (see Table S7 in the online supplement). Effect estimates from the multistate and competing risk models were virtually identical to the estimates from the main analyses (see Table S10 in the online supplement). The multistate models also illustrate that while the risk of psychotic disorders was elevated among depressed patients who progressed first to bipolar disorder, the risk of bipolar disorder was only slightly elevated among depressed patients who progressed first to psychotic disorders, which is in line with the ICD-10 diagnostic hierarchy (see Figure S5 in the online supplement).

DISCUSSION

We examined whether polygenic liabilities for depression, bipolar disorder, and schizophrenia were associated with the risk of progressing to bipolar disorder or psychotic disorders among patients with unipolar depression. We found that after taking the correlations between PRS variables into account, only the PRS for bipolar disorder was associated with progression to bipolar disorder with statistical significance, and only the PRS for schizophrenia was associated with progression to psychotic disorders with statistical significance. These results suggest that the effects of genetic liability on the hazard of progression may be somewhat disorder specific, which is consistent with findings from previous family studies (12, 13), as well as recent results from imaging studies (33). However, it is worth noting that the PRS for schizophrenia was significantly associated with progression to bipolar disorder before adjusting for the other PRS variables and was only partly attenuated (although no longer significant) after mutual adjustment. In contrast, the effect of the PRS for bipolar disorder on the hazard of progression to psychotic disorders was small even before mutual adjustment, and it was close to null thereafter. This suggests that the PRS for bipolar disorder is specifically a risk factor for progression to bipolar disorder, whereas the PRS for schizophrenia may be more generally associated with progression to either outcome. Further investigation is needed to determine how much of this reflects a true association between the PRS for schizophrenia and both outcomes and how much is an artifact of the ICD-10 diagnostic hierarchy, according to which progression from mood to psychotic disorders is more likely to occur than vice versa.

Affective psychotic disorders—that is, a depression or bipolar episode in which psychotic symptoms are present—heuristically straddle the diagnostic divide between mood and psychotic disorders. Consistent with this, we found an interaction between polygenic liability for bipolar disorder and schizophrenia such that high liability for both conferred the greatest risk for affective psychosis, whereas higher liability for one combined with lower liability for the other was associated with decreased risk. This could be interpreted to

mean that the combination of liabilities for both bipolar disorder and schizophrenia produces affective psychotic syndromes, whereas depressed patients with low liability for one but high liability for the other may be transitioning to other outcomes (e.g., nonpsychotic bipolar disorder in the case of individuals with low PRSs for schizophrenia and high PRSs for bipolar disorder). While intriguing, this finding is preliminary and awaits both replication and more in-depth exploration; however, it indicates that studies of the genetics of psychosis should take the affective context into consideration (34).

We sought to evaluate the potential clinical utility of PRS as a tool for helping clinicians identify patients with depression who are at greatest risk for progressing to more severe disorders. The high absolute risk of diagnoses for bipolar and psychotic disorders among individuals with depression compared with the general population highlights the need to screen for bipolar disorder and psychotic symptoms in this patient population. However, our results suggest that parental history is a far more powerful predictor of progression than PRS, particularly for bipolar disorder. Furthermore, it seems that very little of the effect of parental history is mediated by current polygenic scores, and thus the bulk of the parental history effect is likely attributable to a combination of other direct genetic effects (e.g., rare variants, copy number variations, gene-by-gene interactions), indirect genetic effects (e.g., effects of parental genes on the offspring's environment [35]), and nongenetic effects (e.g., increased symptom recognition [23]). This eliminates the possibility that a PRS could be used as a proxy for parental history. However, there may be some predictive capacity to be gained by combining information on both parental history and PRS, along with other clinical predictors. For example, we found that among individuals with a parental history, the PRS enabled us to further differentiate between those with more or less absolute risk of progression, suggesting that PRSs could potentially prove to be useful in some circumstances. Further research, including formal prediction model development and evaluation, is necessary before any definitive conclusions can be reached on the clinical utility of PRSs for predicting conversion to bipolar or psychotic disorders.

Limitations

Several important limitations should be taken into consideration when interpreting these results. First, the study sample did not include individuals treated for depression by general practitioners or private-practice psychiatrists, because diagnostic data for these services are not reported to the DPCRR. Only around 25% of individuals who are medically treated for depression in Denmark receive hospital-based psychiatric care within 5 years of their first antidepressant prescription (36); therefore, our results pertain predominantly to the most severe depression cases. Second, progression was measured using hospital-based contacts, and therefore we were not able to evaluate the presence of subclinical hypomanic, manic, or psychotic symptoms. Thus, our results likely underestimated the true associations between PRS and progression to bipolar and psychotic disorders. Third, the oldest iPSYCH2012 participants were only 35 years old in 2016, and the majority of participants were much younger. Thus, there may be individuals among those classified as not progressing who will receive a diagnosis of bipolar disorder or psychotic disorders in the future. This may also have biased our results toward the null. Fourth, the PRSs for bipolar disorder and schizophrenia used in this study only accounted for a limited fraction of the phenotypic variance of these disorders (30, 31). As results from larger genome-wide association studies become available, prediction of diagnostic progression will likely improve. Finally, to avoid population stratification, the sample was limited to individuals of European ancestry. Consequently, these results may not generalize outside of a Danish or European context. Genetics research as a whole is biased toward discoveries that stand to benefit individuals of European ancestry disproportionately compared with those of other ancestral backgrounds, which has important ethical implications for the field (37).

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