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Relationship of Family Genetic Risk Score With Diagnostic Trajectory in a Swedish National Sample of Incident Cases of Major Depression, Bipolar Disorder, Other Nonaffective Psychosis, and Schizophrenia

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IMPORTANCE Since its inception under Kraepelin in the modern era, diagnostic stability and familial/genetic risk have been among the most important psychiatric nosologic validators.

OBJECTIVE To assess the interrelationships of family genetic risk score (FGRS) with diagnostic stability or diagnostic change in major depression (MD), bipolar disorder (BD), other nonaffective psychosis (ONAP), and schizophrenia.

DESIGN, SETTING, AND PARTICIPANTS This longitudinal population-based cohort (N = 4 171 120) included individuals with incident cases of MD (n = 235 095), BD (n = 11 681), ONAP (n = 16 009), and schizophrenia (n = 6312) who had at least 1 further diagnosis of the 4 disorders during follow-up, as assessed from Swedish national medical registries, observed over a mean (SD) of 13.1 (5.9) years until a mean (SD) age of 48.4 (12.3) years. Data were collected from January 1973 to December 2018, and data were analyzed from August to September 2022.

EXPOSURES FGRS for MD, BD, ONAP, and schizophrenia, calculated from morbidity risks for disorders in first-degree through fifth-degree relatives, controlling for cohabitation effects.

MAIN OUTCOMES AND MEASURES Final diagnostic outcome of MD, BD, ONAP, or schizophrenia.

RESULTS Of 269 097 included individuals, 173 061 (64.3%) were female, and the mean (SD) age at first registration was 35.1 (11.9) years. Diagnostic stability was highest for MD (214 794 [91.4%]), followed by schizophrenia (4621 [73.2%]), BD (7428 [63.6%]), and ONAP (6738 [42.1%]). The second most common final diagnosis for each of these MD, schizophrenia, BD, and ONAP were BD (15 506 [6.6%]), ONAP (1110 [17.6%]), MD (2681 [23.0%]), and schizophrenia (4401 [27.5%]), respectively. A high FGRS for the incident diagnosis was consistently associated with diagnostic stability, while a high FGRS for the final diagnosis and a low FGRS for the incident diagnosis was associated with diagnostic change. In multivariate models, those in the upper 5% of genetic risk had an odds ratio (OR) of 1.75 or greater for the following diagnostic transition: for MD FGRS, ONAP to MD (OR, 1.91; 95% CI, 1.59-2.29) and schizophrenia to MD (OR, 2.45; 95% CI, 1.64-3.68); for BD FGRS, MD to BD (OR, 2.60; 95% CI, 2.47-2.73), ONAP to BD (OR, 2.16; 95% CI, 1.85-2.52), and schizophrenia to BD (OR, 2.20; 95% CI, 1.39-3.49); for ONAP FGRS, MD to ONAP (OR, 1.80; 95% CI, 1.62-2.02), MD to schizophrenia (OR, 1.95; 95% CI, 1.58-2.41), and BD to schizophrenia (OR, 1.89; 95% CI, 1.39-2.56); and for schizophrenia FGRS, MD to schizophrenia (OR, 1.80; 95% CI, 1.46-2.23), and BD to schizophrenia (OR, 1.75; 95% CI, 1.25-2.45). FGRS profiles for incident cases confirmed at final diagnosis were more homogenous than genetic profiles for those who changed diagnoses.

CONCLUSIONS AND RELEVANCE In a large population-based longitudinal cohort, the genetic risk factors for MD, BD, ONAP, and schizophrenia were meaningfully and systematically associated with the diagnostic trajectories of these 4 disorders. Over time, clinical diagnosis and genetic risk profiles became increasingly consilient, thereby providing genetic validation of these diagnostic constructs. Diagnostically unstable incident cases were more genetically heterogeneous than those who were diagnostically stable over time.

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Supplemental content

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The joint investigation of diagnostic stability and genetic risk has been central to empirically based psychiatric nosology since the late 19th century. Kraepelin's research program, foundational to our nosology, was based on observations of the course of psychiatric disorders with the hope that such distinctions would be supported by the results of etiologic research, particularly in brain pathology and genetics.[1] When Robins and Guze[2] proposed their influential model of diagnostic validity of psychiatric disorders, 2 of their 5 criteria were the follow-up study to establish diagnostic stability and the family study to demonstrate the influence of familial and genetic factors.

Predicting diagnostic trajectories is a goal across all of medicine.[3] In this study, in accord with psychiatric tradition, we examine relationships between genetic risk scores and diagnostic trajectories, as has been suggested as one practical application of polygenic risk scores (PRS) in complex diseases.[4,5] Previous studies have shown that in individuals with major depression (MD), high genetic risk for bipolar disorder (BD) is related to the risk for subsequently transitioning to BD.[6-12] Furthermore, schizophrenia PRS in both the Suffolk County Mental Health Project[13] and the Danish iPsych cohort[10] predicted progression from affective illness to a nonaffective psychosis.

We here expand on previous reports, examining in a Swedish national sample the diagnostic trajectories of incident cases of 4 major psychiatric disorders: MD, BD, other nonaffective psychosis (ONAP), and schizophrenia. Individuals were observed over a mean (SD) of 13.1 (5.9) years. For each disorder, we explore the degree to which profiles of genetic risk were associated with the diagnostic stability and specific diagnostic changes for these disorders. We then compare the genetic profiles of the incident and final cases of the 4 disorders.

Key Points

Question Is family genetic risk score associated with individuals' diagnostic stability (ie, change in major depression, bipolar disorder, other nonaffective psychosis, and schizophrenia diagnoses)?

Findings In this population-based cohort study including 269 097 individuals, incident and final diagnoses of these 4 disorders were examined over a mean of 13 years. A high genetic risk for the incident diagnosis was associated with diagnostic stability, while high genetic risk for the final diagnosis and low genetic risk for the incident diagnosis was associated with diagnostic change.

Meaning In this population-based cohort, the genetic risk factors for major depression, bipolar disorder, other nonaffective psychosis, and schizophrenia were systematically associated with their diagnostic trajectories.

Methods

We collected information on individuals from Swedish population-based registers with national coverage linking each person's unique personal identification number (replaced with a pseudonymized serial number by Statistics Sweden to preserve confidentiality). Ethical approval was granted by the regional ethical review board in Lund. Participant consent was waived because deidentified data were used. The database consisted of all individuals born in Sweden from 1950 to 1995 to Swedish-born parents through December 31, 2018. The database included first diagnosis of MD, BD, ONAP, and schizophrenia. Codes for these disorders from *International Classification of Diseases, Eighth Revision* (*ICD-8*), *ICD-9*, and *ICD-10* were reported in primary care, specialist, and hospital registries (eAppendix and eTable 1 in Supplement 1). Registrations for the same diagnosis within 30 days of the first registration were censored from analysis. The outcome variable was the last diagnosis, assuming that it was based on the maximal amount of diagnostic information. We included family genetic risk scores (FGRS) for MD, BD, ONAP, and schizophrenia. The FGRSs are calculated from morbidity risks for disorders in first-degree through fifth-degree relatives, controlling for cohabitation effects, and thus arise from phenotypes in extended pedigrees, not from molecular genetic data (eTable 2 in Supplement 1). All the FGRS analyses are also controlled for year of birth and number of years of follow-up.

We present the mean FGRSs with 95% CIs for the 4 outcomes for each of the initial diagnostic categories. For analysis, we used multinomial regression, by initial diagnostic category, using those who remained diagnostically stable as reference. These models included the 4 FGRSs, sex, year of birth, and age at registration for the initial diagnosis. We categorized the FGRSs into 20 equally sized groups (based on the population born from 1950 to 1995). To capture the range of the diagnostic outcomes associated with the upper portions of the FGRS distributions, we present odds ratios (ORs) for 3 levels of percentile scores: 86th to 90th, 91st to 95th, and 96th to 100th. The reference was those with the lowest FGRS (1st to 50th percentile). We used pairwise 2-tailed *t* tests for the comparison of the mean FGRSs. We used $P < .05$ as the level for statistical significance if nothing else is noted. Analyses were conducted using SAS version 9.4 (SAS Institute).

Results

Descriptive Statistics

From the national cohort of 4 171 120 individuals, we selected individuals with an incident diagnosis of MD, BD, ONAP, or schizophrenia from age 15.4 to 62.9 years (**Table 1**). These individuals had to have at least 1 additional diagnosis of 1 or more of these disorders and at least 7 years of follow-up data from their first diagnosis. Of 269 097 identified individuals, 173 061 (64.3%) were female, and the mean (SD) age at first registration was 35.1 (11.9) years. As illustrated in **Figure 1**, the samples of incident diagnoses varied from 6312 individuals with schizophrenia to 235 095 individuals with MD. Given the narrow Swedish diagnostic view of schizophrenia, cases of incident ONAP (n = 16 009) substantially outnumbered those with schizophrenia. There was a higher preponderance of female sex among those with MD and BD and a higher preponderance of male sex among those with schizophrenia. We observed the sample for a mean (SD) of 13.1 (5.9) years until a mean

Table 1. Descriptive Statistics for Database Consisting of 4 171 120 Individuals Born in Sweden From 1950 to 1995 to Swedish-Born Parents Followed Up through December 31, 2018

	No. (%)				
		First diagnosis			
Measure	Total sample	MD	BD	ONAP	Schizophrenia
Total, No.	269 097	235 095	11 681	16 009	6312
Sex					
Female	173 061 (64.3)	156 656 (66.6)	6834 (58.5)	7579 (47.3)	1992 (31.6)
Male	96 036 (35.7)	78 439 (33.4)	4847 (41.5)	8430 (52.7)	4320 (68.4)
Year of birth, mean (SD)	1970 (12.3)	1971 (12.3)	1968 (12.6)	1966 (11.0)	1961 (7.7)
First registration, mean (SD)					
Age, y	35.1 (11.9)	35.7 (12.0)	32.3 (11.2)	31.2 (9.9)	29.2 (9.0)
Year	2005 (6.3)	2006 (4.2)	2000 (10.9)	1998 (9.2)	1990 (10.4)
Years of follow-up after first registration, mean, (SD)	NA	12.0 (4.0)	17.7 (10.3)	19.9 (8.8)	26.3 (10.4)
Last diagnosis					
MD	NA	214 794 (91.4)	2681 (23.0)	2761 (17.3)	375 (5.9)
BD	NA	15 506 (6.6)	7428 (63.6)	2109 (13.2)	206 (3.3)
ONAP	NA	3816 (1.6)	1091 (9.3)	6738 (42.1)	1110 (17.6)
Schizophrenia	NA	979 (0.4)	481 (4.1)	4401 (27.5)	4621 (73.2)

Abbreviations: BD, bipolar disorder; MD, major depression; NA, not applicable; ONAP, other nonaffective psychosis.

(SD) age of 48.4 (12.3) years. For initial and final diagnoses by sex, age at initial diagnosis, and follow-up period, see eTable 3 in Supplement 1. The diagnostic groups differ in mean year of registration and follow-period because coverage for inpatient diagnoses have existed longer in Sweden than for outpatient and primary care diagnoses. We account for these effects by controlling for year of birth in all FGRS models.

For all disorders, the most common final diagnosis was the initial diagnosis. Diagnostic stability was highest for MD (214 794 [91.4%]), followed by schizophrenia (4621 [73.2%]), BD (7428 [63.6%]), and ONAP (6738 [42.1%]). The second most common final diagnosis for each of these MD, schizophrenia, BD, and ONAP were BD (15 506 [6.6%]), ONAP (1110 [17.6%]), MD (2681 [23.0%]), and schizophrenia (4401 [27.5%]), respectively.

Primary Results

Figure 1 presents the mean FGRS for the 4 possible diagnostic outcome groups for each of our diagnoses (eTable 4 in Supplement 1). For example, Figure 1A presents individuals with an initial diagnosis of MD who had each of the 4 possible final diagnoses: MD (ie, diagnostic stability) and a diagnostic change to BD, ONAP, or schizophrenia. Figure 1B-D present parallel results for those with an initial diagnosis of BD, ONAP, and schizophrenia, respectively. Given differences in sample sizes for the 16 combinations of initial and final diagnoses, precision of the FGRS estimates varied widely, as reflected in the size of 95% CIs.

Effect sizes and Bonferroni-corrected *P* value comparisons across the FGRS scores are presented in **Table 2**. For individuals with an incident diagnosis of MD, the 4 diagnostic outcome groups had distinct FGRS profiles, with 18 of 24 comparisons differing significantly. The highest FGRS in each of the 4 outcome groups were for the final diagnosis (eg, MD FGRS highest in diagnostically stable cases, while the BD FRGS, ONAP FRGS, and schizophrenia FRGS was highest in those who converted to BD, ONAP, and schizophrenia, respectively) (Figure 1A). The MD to ONAP transition group stood out as having a similar moderate elevation across all 4 FGRSs.

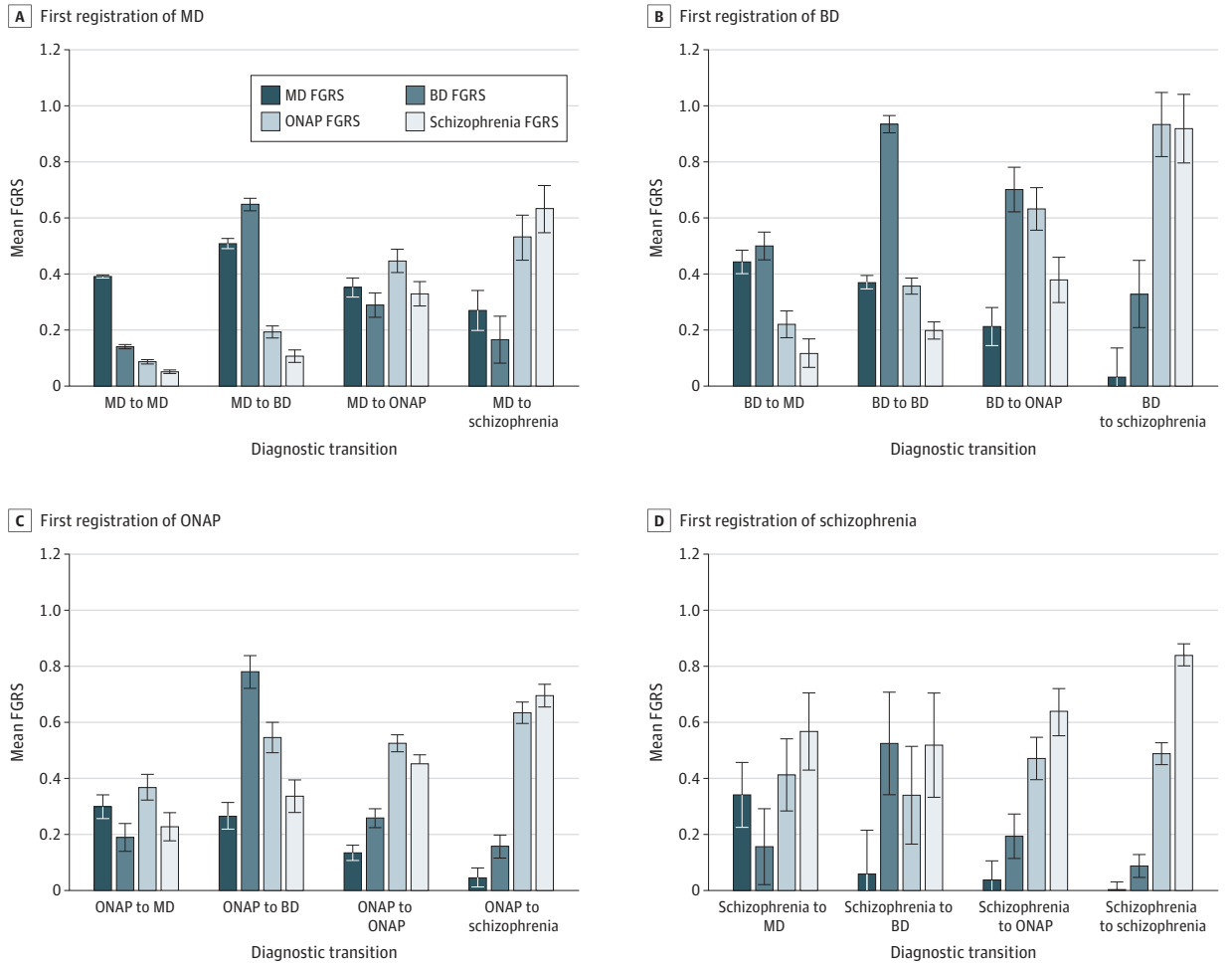
The FGRS profile was also distinctive for each of the 4 outcome groups for BD (Figure 1B). The profile of those who were diagnostically stable was dominated by a strong elevation in BD FGRS, while the profile of those who transitioned from BD to schizophrenia was notable for quite high levels of ONAP FGRS and schizophrenia FGRS. The most notable pattern in the outcome groups for ONAP (Figure 1C) was the mirror image of the FGRS for BD, ONAP, and schizophrenia in the genetic profiles for the ONAP to BD vs the ONAP to schizophrenia transition groups. All 4 of the outcome groups for those with an initial diagnosis of schizophrenia (Figure 1D) had substantial elevations of schizophrenia FRGS, with the largest differences seen in the levels of MD FRGS, which had a monotonic substantial decline across the 4 outcome groups, and BD FRGS, which was highest in the BD outcome, intermediate for the MD and ONAP outcome, and lowest in the schizophrenia outcome group.

FGRS and Diagnostic Change

Figure 2 presents the results of the multivariate model of diagnostic transitions, which compared individuals with incident cases who changed diagnosis with those who remained diagnostically stable. These models depict the unique relationships of each FGRS accounting for the other FGRSs. In each case, we examined 3 levels of scores against the lowest half of the FGRS distribution (1 to 50th percentile) for those in the moderately high (86th to 90th percentile), high (91st to 95th percentile), and very high (96th to 100th percentile) genetic risk. The y-axis represents ORs for the impact of these high FGRS compared with those with the lowest 50%.

In Figure 2A, which depicts diagnostic changes for individuals with incident MD, MD FGRS was not associated with diagnostic transition, with 1 exception: a high MD FGRS significantly reduced risk for a transition to schizophrenia. A different picture was seen with the BD FGRS, where BD FGRS was associated with an MD to BD transition, with those at very high genetic risk having a nearly 3-fold increased risk of develop-

Figure 1. Mean Family Genetic Risk Scores (FGRS) for Individuals With Incident Major Depression (MD), Bipolar Disorder (BD), Other Nonaffective Psychosis (ONAP), and Schizophrenia With MD, BD, ONAP, or Schizophrenia as a Function of Their Final Diagnosis



The mean standardized FGRS for MD, BD, ONAP, and schizophrenia for individuals with incident cases of each disorder. Thus, an FGRS score of 0 indicates the population mean and an FGRS score of 1 indicates 1 SD greater than the population mean. The statistical differences between the FGRS are presented in Table 2. Error bars indicate 95% CIs.

ing BD. Very high levels of FGRS for both ONAP and schizophrenia approximately doubled the risk of a final diagnosis of ONAP or schizophrenia, respectively.

In those with a first BD registration (Figure 2B), a high or very high MD FGRS modestly increased the risk for a BD to MD conversion. By contrast, a very high BD FGRS was associated with a significantly reduced probability of a diagnostic conversion to MD, ONAP, or schizophrenia. Very high levels of both ONAP FGRS and schizophrenia FGRS significantly increased the risk of a diagnostic change from BD to ONAP, while only a very high schizophrenia FGRS was significantly associated with an increase in risk of a diagnostic conversion to schizophrenia.

In individuals with an initial diagnosis of ONAP (Figure 2C), elevated levels of MD FGRS increased the risk of a transition to MD and deceased the risk of a transition to schizophrenia. Very high levels of BD FGRS significantly decreased the probability of a conversion to MD or schizophrenia and increased the risk of developing BD. Levels of ONAP FGRS were not associated with diagnostic change, while very high levels of schizophrenia FGRS reduced conversion rates to MD and BD and increased rates of an ONAP to schizophrenia transition.

Finally, in individuals with an initial diagnosis of schizophrenia (Figure 2D), high levels of MD FGRS significantly increased the risk of a schizophrenia to MD transition more than 2-fold, while very high levels of BD FGRS roughly doubled the risk of developing BD. Likely because of limited statistical power, high levels of the FGRS for ONAP and schizophrenia were not associated with diagnostic conversions.

Comparison of Confirmed and Not Confirmed Incident Cases

We examined the FGRS profiles of the 4 incident disorders and then the subsets of individuals whose final diagnoses were confirmed vs not confirmed, meaning that the final diagnosis was or was not concordant with the first diagnosis (**Figure 3**). Compared with those with confirmed cases, those

Table 2. Difference in Family Genetic Risk Score (FGRS) for Tests of Equality for FGRS Scores Across the 4 Possible Final Diagnoses Within the 4 Initial Diagnostic Groups

Group	Mean standardized FGRS (95% CI)			
	MD FGRS	BD FGRS	ONAP FGRS	Schizophrenia FGRS
Initial diagnosis of MD				
MD to BD transition	−0.11 (−0.15 to −0.08)[a]	−0.51 (−0.55 to −0.47)[a]	−0.11 (−0.14 to −0.07)[a]	−0.06 (−0.09 to −0.02)[a]
MD to ONAP transition	0.04 (−0.02 to 0.10)	−0.15 (−0.22 to −0.07)[a]	−0.36 (−0.43 to −0.29)[a]	−0.28 (−0.35 to −0.20)[a]
MD to schizophrenia transition	0.12 (0 to 0.24)	−0.02 (−0.17 to 0.12)	−0.44 (−0.58 to −0.30)[a]	−0.58 (−0.73 to −0.43)[a]
BD to ONAP transition	0.16 (0.08 to 0.23)[a]	0.36 (0.28 to 0.44)[a]	−0.25 (−0.33 to −0.17)[a]	−0.22 (−0.31 to −0.14)[a]
BD to schizophrenia transition	0.24 (0.11 to 0.37)[a]	0.48 (0.33 to 0.63)[a]	−0.34 (−0.48 to −0.19)[a]	−0.53 (−0.68 to −0.37)[a]
ONAP to schizophrenia transition	0.08 (−0.06 to 0.22)	0.12 (−0.04 to 0.29)	−0.08 (−0.24 to 0.07)	−0.30 (−0.47 to −0.14)[a]
Initial diagnosis of BD				
MD to BD transition	0.07 (−0.01 to 0.16)	−0.44 (−0.54 to −0.33)[a]	−0.14 (−0.23 to −0.04)[a]	−0.08 (−0.19 to 0.02)
MD to ONAP transition	0.23 (0.09 to 0.37)[a]	−0.20 (−0.37 to −0.04)[a]	−0.41 (−0.57 to −0.26)[a]	−0.26 (−0.43 to −0.09)[a]
MD to schizophrenia transition	0.41 (0.22 to 0.61)[a]	0.17 (−0.06 to 0.40)	−0.72 (−0.93 to −0.50)[a]	−0.80 (−1.04 to −0.57)[a]
BD to ONAP transition	0.16 (0.03 to 0.28)[a]	0.23 (0.08 to 0.38)[a]	−0.28 (−0.42 to −0.13)[a]	−0.18 (−0.33 to −0.03)[a]
BD to schizophrenia transition	0.34 (0.15 to 0.52)[a]	0.61 (0.39 to 0.82)[a]	−0.58 (−0.79 to −0.37)[a]	−0.72 (−0.94 to −0.50)[a]
ONAP to schizophrenia transition	0.18 (−0.03 to 0.39)	0.37 (0.12 to 0.62)[a]	−0.30 (−0.54 to −0.06)[a]	−0.54 (−0.80 to −0.29)[a]
Initial diagnosis of ONAP				
MD to BD transition	0.03 (−0.08 to 0.15)	−0.59 (−0.73 to −0.46)[a]	−0.18 (−0.31 to −0.05)[a]	−0.11 (−0.24 to 0.03)
MD to ONAP transition	0.17 (0.08 to 0.25)[a]	−0.07 (−0.17 to 0.03)	−0.16 (−0.26 to −0.06)[a]	−0.23 (−0.33 to −0.12)[a]
MD to schizophrenia transition	0.25 (0.16 to 0.35)[a]	0.03 (−0.08 to 0.14)	−0.27 (−0.37 to −0.16)[a]	−0.47 (−0.58 to −0.36)[a]
BD to ONAP transition	0.13 (0.03 to 0.23)[a]	0.52 (0.41 to 0.64)[a]	0.02 (−0.09 to 0.13)	−0.12 (−0.23 to 0)
BD to schizophrenia transition	0.22 (0.12 to 0.32)[a]	0.63 (0.50 to 0.75)[a]	−0.09 (−0.20 to 0.03)	−0.36 (−0.48 to −0.24)[a]
ONAP to schizophrenia transition	0.09 (0.01 to 0.16)	0.10 (0.01 to 0.19)	−0.11 (−0.19 to −0.02)[a]	−0.24 (−0.33 to −0.15)[a]
Initial diagnosis of schizophrenia				
MD to BD transition	0.28 (−0.06 to 0.62)	−0.37 (−0.76 to 0.03)	0.07 (−0.31 to 0.45)	0.05 (−0.35 to 0.45)
MD to ONAP transition	0.30 (0.07 to 0.54)[a]	−0.04 (−0.31 to 0.24)	−0.06 (−0.32 to 0.20)	−0.07 (−0.35 to 0.21)
MD to schizophrenia transition	0.34 (0.13 to 0.55)[a]	0.07 (−0.18 to 0.31)	−0.08 (−0.31 to 0.16)	−0.27 (−0.52 to −0.02)[a]
BD to ONAP transition	0.02 (−0.28 to 0.32)	0.33 (−0.02 to 0.68)	−0.13 (−0.46 to 0.20)	−0.12 (−0.47 to 0.23)
BD to schizophrenia transition	0.06 (−0.22 to 0.34)	0.44 (0.11 to 0.76)[a]	−0.15 (−0.46 to 0.16)	−0.32 (−0.65 to 0.01)
ONAP to schizophrenia transition	0.04 (−0.09 to 0.17)	0.11 (−0.05 to 0.26)	−0.02 (−0.16 to 0.13)	−0.20 (−0.35 to −0.04)[a]

Abbreviations: BD, bipolar disorder; MD, major depression; ONAP, other nonaffective psychosis.

[a] Significant at Bonferroni-corrected $P < .0005$ (.05/96 tests).

with unconfirmed cases of MD had significantly higher levels of all 4 FRGS, while those with unconfirmed BD had significantly lower levels of BD FGRS and higher levels of schizophrenia FGRS. Individuals with unconfirmed cases of ONAP had significantly higher levels of MD FGRS and BD FGRS than those with confirmed cases. Compared with individuals with confirmed cases of schizophrenia, those with unconfirmed cases had significantly lower levels of schizophrenia FGRS and higher levels of MD FGRS and BD FGRS.

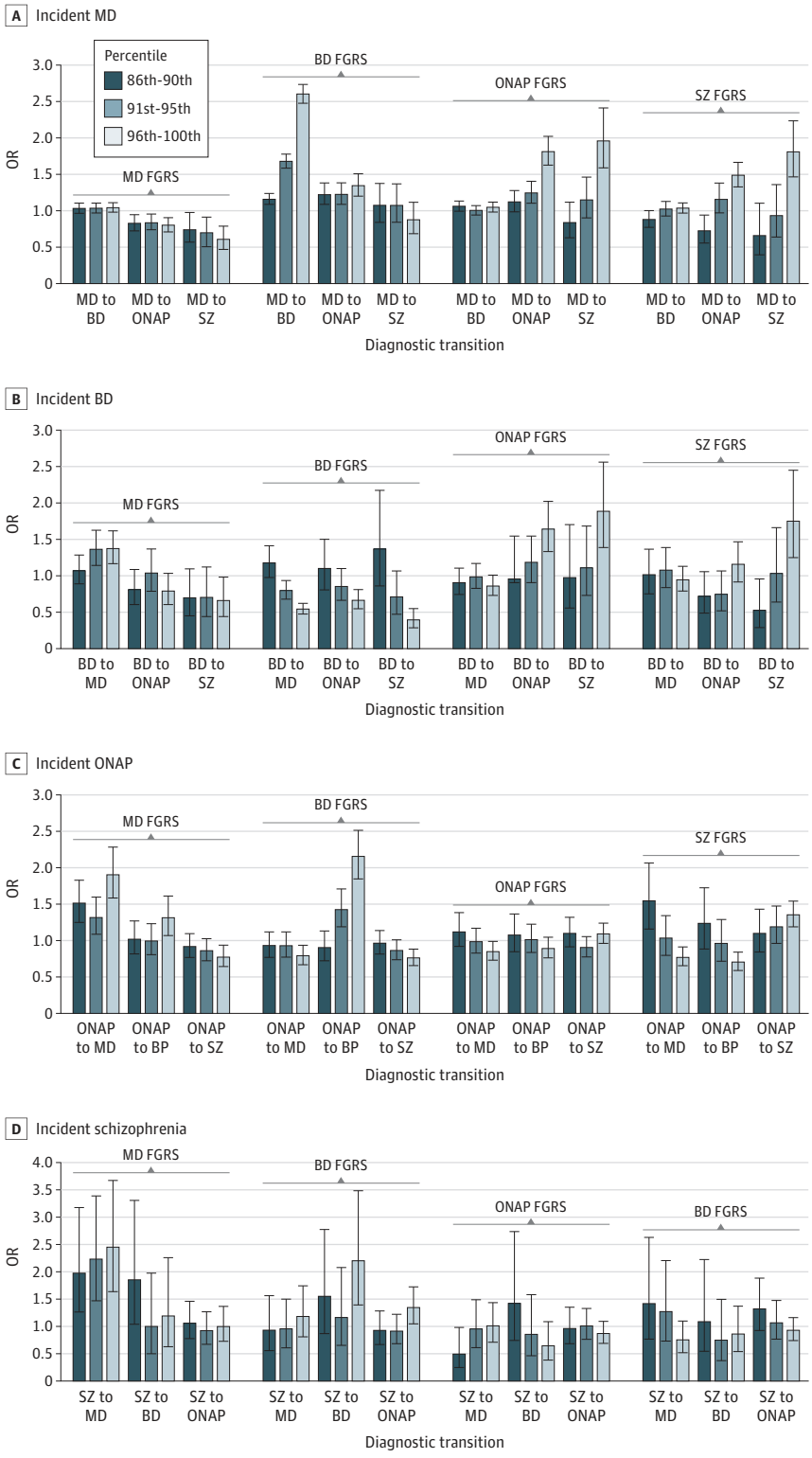
Discussion

Using a national Swedish sample of incident cases of 4 psychiatric disorders—MD, BD, ONAP, and schizophrenia—we assessed whether the patterns of genetic risks for these disorders were associated with diagnostic trajectories over a 13-year follow-up period. Consistent with smaller prior studies,[6-13] we showed substantial associations between the genetic risk profiles and diagnostic trajectories. Of our many specific findings, we emphasize 8.

First, for individuals with an initial diagnosis of disorder A, a high FGRS for disorder B was associated with an A to B diagnostic change. This was seen clearly for BD, where BD FGRS was the strongest genetic risk factor for individuals with MD to BD, ONAP to BD, and schizophrenia to BD conversions, with the same pattern evident for schizophrenia. This trend was weakest with MD FGRS.

Second, among individuals with an initial diagnosis of BD, OPAP, and schizophrenia, a low MD FGRS was associated with a final psychotic disorder diagnosis.

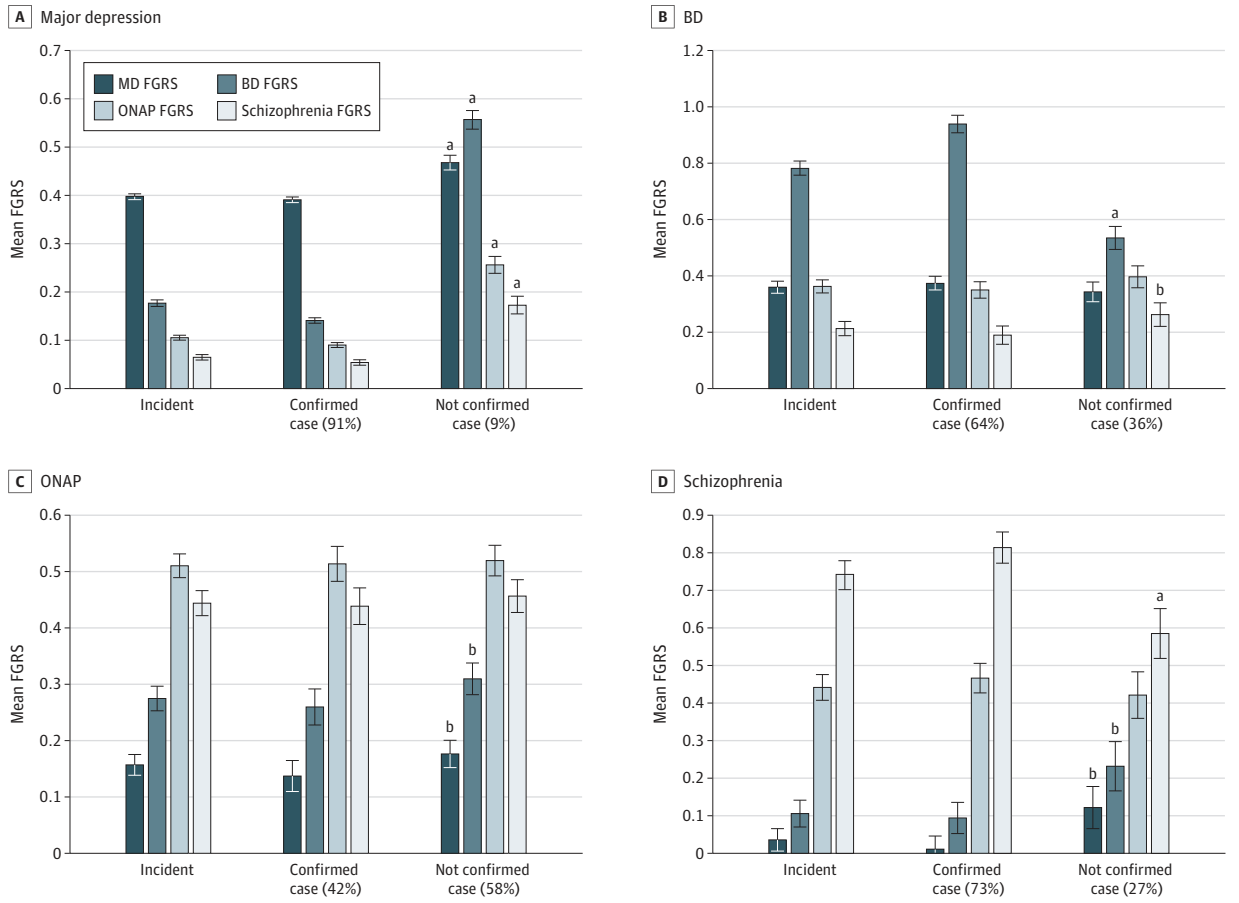
Figure 2. Odds Ratios (ORs) From a Multinomial Regression Model



Multinomial regression models predicting diagnostic change for individuals with incident major depression (MD), bipolar disorder (BD), other nonaffective psychosis (ONAP), and schizophrenia (SZ). Models are controlled for year of birth, age at registrations, and sex for 3 levels of elevated family genetic risk scores (FGRS): 86th to 90th percentile, 91st to 95th percentile, and 96th to 100th percentile. The reference for these calculations is the FGRS from the 1st to 50th percentile of the distribution. Error bars indicate 95% CIs.

Third, ONAP had a pattern of genetic risks intermediate between those of BD and schizophrenia. For each 4 initial diagnoses, those with a final diagnosis of ONAP had a higher BD FGRS and a lower schizophrenia FGRS than those with a final diagnosis of schizophrenia. For individuals with an initial diagnosis of MD, BD, and schizophrenia, those with a final diagnosis of ONAP vs BD had a lower BD $FGRS_{BD}$ and a higher schizophrenia FGRS.

Figure 3. Comparison of Individuals With Confirmed and Not Confirmed Incident Cases of Major Depression (MD), Bipolar Disorder (BD), Other Nonaffective Psychosis (ONAP), and Schizophrenia



The family genetic risk score (FGRS) profiles (consisting of FGRS for MD, BD, ONAP, and schizophrenia) for all individuals with incident cases, individuals with incident cases that were diagnostically stable (ie, with the incident diagnosis confirmed by the final diagnosis), and individuals with incident cases that were not diagnostically stable (ie, with the incident diagnosis not confirmed by the final diagnosis).

[a] Significant at Bonferroni-corrected $P < .003$ (.05/16 tests).

[b] $P < .05$.

Fourth, the genetic profiles of cases based on final diagnosis were substantially influenced by their initial diagnosis. For example, compared with individuals with diagnostically stable MD, level of BD FGRS were much higher in those with BD to MD conversion while levels of ONAP FGRS and schizophrenia FGRS were substantially greater in those with ONAP to MD conversion and schizophrenia to MD conversion, respectively.

Fifth, comparing those with an opposite course of illness, the genetic profile of those with BD to ONAP conversion was similar to those with an ONAP to BD pattern. However, this was not found for BD to schizophrenia conversion and schizophrenia to BD conversion, where the former had considerably higher levels of ONAP FGRS and schizophrenia FGRS and somewhat lower levels of BD FGRS than the latter.

Sixth, the strongest relationship was seen for individuals who had an FGRS in the upper 5% to 10% of the population. This pattern has been observed in prior PRS analyses.[14,15]

Seventh, the magnitude of increased risks seen in our analyses—typically maximizing at ORs around 2.0—while of research interest, are unlikely to be clinically actionable. Whether new and larger samples using FGRS or PRS scores and/or novel statistical approaches will increase power sufficiently to produce clinically relevant predictions remains to be seen but is a topic of considerable interest.

Eighth, in comparing those with confirmed and unconfirmed cases for all 4 of the conditions, those with confirmed cases presented purer genetic profiles, demonstrating higher relative levels for their own FGRS compared with that of other disorders.

Of the prior efforts to associate genetic risk and diagnostic trajectory in psychiatric illness, this study most closely resembles that of Musliner et al.[10] They included nearly 17 000 individuals with MD for a median of 7 years and predicted diagnostic change from PRSs for MD, BD, and schizophrenia. Congruent with our findings, the PRSs for BD and

schizophrenia predicted progression to BD and nonaffective psychosis, respectively.

Limitations

These results should be interpreted in the context of 9 potential methodological limitations. First, the validity of our analyses depends on the quality of diagnoses in the Swedish national registries, which for hospital diagnoses for schizophrenia and BD have been well supported.[16-18] The validity of MD diagnoses is supported by its prevalence, sex ratio, sibling and twin correlations, and associations with known psychosocial risk factors.[19,20] We are unaware of published evaluations of the validity of our ONAP diagnosis.

Second, the main analyses presented combined male and female individuals, although we know that the 4 disorders vary rather widely in their risk by sex. We repeated all the analyses in Figure 1 by male and female sex separately and present these findings in eFigure 1 and eTable 5 in Supplement 1. These results are reassuring in that they revealed very few notable differences in results across sexes.

Third, our primary analyses required only a single instance of the initial and final diagnoses. To reduce the chances that one of these diagnoses was an outlier, we repeated all of analyses requiring a minimum of 2 separate instances of the initial and final diagnosis diagnoses (eFigure 2 in Supplement 1). These results show very similar patterns to those reported above.

Fourth, the FGRS, a family phenotype-based method to assess quantitative genetic risk, has been now widely published,[21-27] with prior reports demonstrating that this score is not highly sensitive to the various assumptions involved in its calculation, that the correction for cohabitation effects performs appropriately, and the method agrees well with other similar, although statistically distinct, approaches.[28]

Fifth, ONAP is a broad syndromal designation, not a specific psychiatric diagnosis. In eTable 6 in Supplement 1, we show that only 3 subcategories (*ICD-10* codes F22 [persistent delusional disorders], F23 [acute and transient psychotic disorders], and F29 [unspecified nonorganic psychosis]) had more than 1500 incident cases with *ICD-10* diagnoses and thus could be meaningfully examined. Their FGRS profiles are presented in eFigure 3 in Supplement 1 and were relatively similar, differing significantly in only 2 of 16 comparisons (eTable 7 in Supplement 1).

Sixth, we excluded individuals from analysis with a single diagnosis during our follow-up period. As seen in eFigure 4 in Supplement 1, across all 4 of the disorders, such individuals typically had FGRS scores substantially lower than those with 2 or more diagnoses.

Seventh, we did not examine diagnoses obtained between the first and last diagnosis. Such diagnoses were relatively common (eFigure 5 in Supplement 1) and associated in expected ways with FGRS profiles (eFigure 6 in Supplement 1). For example, the BD FGRS was higher in individuals with an incident MD and final BD diagnosis if additional BD diagnoses occurred in the interim. We only examined 4 psychiatric disorders and so cannot comment on the relationship between FGRS and the many patterns of diagnostic trajectories that would be seen across other psychopathological domains.

Eighth, we combined for analyses individuals first diagnosed in hospital, specialist, and primary care settings. As seen in eTable 8 in Supplement 1, diagnostic stability by site of first registration varied most for MD, being highest and lowest for individuals initially diagnosed in primary care and inpatient settings, respectively.

Ninth, could physician knowledge of the patient's family history influence the diagnostic change in these individuals? This could most likely impact our results when, in between a an individual's incident and final diagnosis, a first-degree relative (the kind most likely known to the treating physician) had an onset of the disorder subsequently assigned to the individual (eg, an individual with an MD to BD trajectory had a sibling develop BD in between the initial MD and subsequent BD diagnosis). This occurred 1688 times in this cohort (eTable 9 in Supplement 1). When we censored all those relatives from the FGRS, only modest changes were observed in our key results (eFigure 7 in Supplement 1). But we cannot rule out other ways in which the diagnoses might be biased by the physician's knowledge of the patient's family history.

Conclusions

As predicted by Kraepelin, in this large-scale population-based longitudinal cohort study, the genetic risk factors for 4 major psychiatric disorders—MD, BD, ONAP, and schizophrenia—were meaningfully and systematically related to diagnostic trajectories. Furthermore, when observed over time, clinical diagnosis and genetic risk profiles became increasingly consilient, thereby providing genetic validation of these diagnostic constructs. Our findings demonstrate the added value of studying patients a decade into their course of illness, as genetic studies of incident cases would produce considerably noisier findings, including higher cross-disorder genetic correlations.

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