Original Investigation

Patterns of Nonrandom Mating Within and Across 11 Major Psychiatric Disorders

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IMPORTANCE Psychiatric disorders are heritable, polygenic traits, which often share risk alleles and for which nonrandom mating has been suggested. However, despite the potential etiological implications, the scale of nonrandom mating within and across major psychiatric conditions remains unclear.

OBJECTIVE To quantify the nature and extent of nonrandom mating within and across a broad range of psychiatric conditions at the population level.

DESIGN, SETTING, AND PARTICIPANTS Population-based cohort using Swedish population registers. Participants were all Swedish residents with a psychiatric diagnosis of interest (attention-deficit/hyperactivity disorder, autism spectrum disorder, schizophrenia, bipolar disorder, major depression, generalized anxiety disorder, agoraphobia, social phobia, obsessive-compulsive disorder, anorexia, or substance abuse), along with their mates. Individuals with select nonpsychiatric disorders (Crohn's disease, type 1 and type 2 diabetes mellitus, multiple sclerosis, or rheumatoid arthritis) were included for comparison. General population samples were also derived and matched 1:5 with each case proband. Inpatient and outpatient diagnostic data were derived from the Swedish National Patient Register (1973-2009), with analyses conducted between June 2014 and May 2015.

MAIN OUTCOMES AND MEASURES Correlation in the diagnostic status of mates both within and across disorders. Conditional logistic regression was used to quantify the odds of each diagnosis in the mates of cases relative to matched population controls.

RESULTS Across cohorts, data corresponded to 707 263 unique case individuals, with women constituting 45.7% of the full population. Positive correlations in diagnostic status were evident between mates. Within-disorder correlations were marginally higher (range, 0.11-0.48) than cross-disorder correlations (range, 0.01-0.42). Relative to matched populations, the odds of psychiatric case probands having an affected mate were significantly elevated. Differences in the magnitude of observed relationships were apparent by disorder (odds ratio range, 0.8-11.4). The number of comorbidities in a case proband was associated with the proportion of affected mates. These relationships were not apparent or weaker in magnitude among nonpsychiatric conditions (correlation range, −0.03 to 0.17).

CONCLUSIONS AND RELEVANCE Nonrandom mating is evident in psychiatric populations both within specific disorders and across the spectrum of psychiatric conditions. This phenomenon may hold important implications for how we understand the familial transmission of these disorders and for psychiatric genetic research.

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Editorial

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The term *marital resemblance* refers to the observed tendency for mated pairs to be more phenotypically similar for a given characteristic than would be expected by chance.[1] A modest body of literature has suggested the presence of marital resemblance for a range of psychiatric features[2-5] and clinical diagnoses,[6-8] with a small subset of this work noting resemblance across disorders.[9,10] However, the limited range of conditions considered within these investigations and their collective reliance on small volunteer samples and self- or informant reports highlights the need for work that can assess this phenomenon in larger, more diverse psychiatric populations.

Psychiatric disorders are thought to stem from a complex interplay between genetic and environmental risk factors, with the magnitude of their respective influence varying by disorder, sex, and time.[11,12] In this context, spousal resemblance becomes an important phenomenon because the pairing of individuals with a psychiatric condition (a complex trait) at a rate greater than chance would have population-level effects on each of these determinant factors: increasing the genetic variance of these offspring (from the population mean) while also producing familial environments that are more likely to be shaped by the relevant conditions.[13,14] In this manner, if present, nonrandom mating could have important implications for our understanding of the transmission and persistence of psychiatric illness. Known overlaps in the genetic risks for psychiatric disorders only add to this rationale[15-18] and underscore the need to extend such examination to cross-disorder mating patterns.

The primary aim of the present study was, therefore, to extend work in this area and determine the extent to which nonrandom mating is present within and across a broad range of psychiatric conditions at the population level.

Key Points

Question: What is the nature and extent of nonrandom mating in psychiatric populations, and to what degree does it vary by disorder?

Findings: Nonrandom mating was widespread in psychiatric populations both within and across psychiatric disorders but was not observed in nonpsychiatric populations.

Meaning: This phenomenon may hold important implications for how we understand the familial transmission of psychiatric disorders and for genetic research.

Methods

National Registers and Sample Identification

Ethical approval was obtained from the research ethics committee at Karolinska Institutet, Stockholm, Sweden. The requirement for informed consent was waived because the study was register based and the included individuals were deidentified. Data were linked across 3 Swedish national registers using unique personal identification numbers that have been assigned at birth in Sweden since 1947. The study dates were defined by the psychiatric outcomes of the population as defined using the Swedish National Patient Register (NPR), with analyses conducted between June 2014 and May 2015.

The NPR includes diagnostic information on all individuals admitted to a Swedish hospital, with complete nationwide psychiatric records from 1973. Since 2001, the NPR has also contained data on outpatient consultations, including psychiatric care. Each consultation is recorded as a unique entry in the NPR, with a corresponding discharge diagnosis (as determined by the treating physician). These diagnoses are documented using the World Health Organization's *International Statistical Classification of Diseases and Related Health Problems*, including *ICD-8* (1969-1986), *ICD-9* (1987-1996), and *ICD-10* (1997 onward). This register has been heavily used in research, leading to standardized and validated protocols for selecting psychiatric populations. These protocols have been adhered to in the present investigation, with established codes (eMaterial in the Supplement) used to define cases of the following: schizophrenia,[19] bipolar disorder,[19] autism spectrum disorder (ASD),[19] anorexia nervosa,[19] substance abuse,[19] attention-deficit hyperactivity disorder (ADHD),[15] obsessive-compulsive disorder (OCD),[20] major depressive disorder (MDD),[19] social phobia, agoraphobia,[21] and generalized anxiety disorder (GAD).[21] Individuals with tic disorder were also selected, although small case numbers precluded examination of mating patterns in these populations. For purposes of comparison, cases of select nonpsychiatric conditions of similar incidence and age at onset were also identified, including Crohn's disease,[22] type 1 and type 2 diabetes mellitus, multiple sclerosis,[23] and rheumatoid arthritis.[24,25]

Case probands were defined as any individual with a diagnosis of interest as indicated by at least 1 relevant *ICD* diagnosis (2 for schizophrenia and bipolar disorder) registered in the NPR. These diagnoses were identified using a nonhierarchical structure. Therefore, an individual with multiple diagnoses (eg, ASD and OCD) was permitted to appear as a "case" in both the ASD and OCD data sets. To each case proband, we matched 5 population controls on the basis of age, sex, and area of residence in Sweden at the time of the proband's first diagnosis.

Mating relationships were identified through (1) a record of an individual's marriage (Total Population Register, which contains demographic information [eg, sex and marital status] for all individuals born or living in Sweden, with complete coverage from 1968 onward) or (2) a record of an individual being the biological parent of a child in the Multi-Generation Register. Because many couples in Sweden remain in unregistered, cohabitating relationships, the use of the birth of a child was integral to capturing Sweden's true "mated" population. Although imperfect, this process has ensured inclusion of the largest possible segment of these individuals. In the Multi-Generation Register, the father is defined as the spouse at the time of the child's birth or, alternatively, the individual acknowledged as the father. Due to the register's emphasis on biological relationships in recording parentage, all pairs included in the present study were heterosexual.

For each member of a mated case pair, a comparison sample was again generated and matched 1:5 on age, sex, and county of residence. The matching criteria also specified that population controls must not have the diagnosis of interest.

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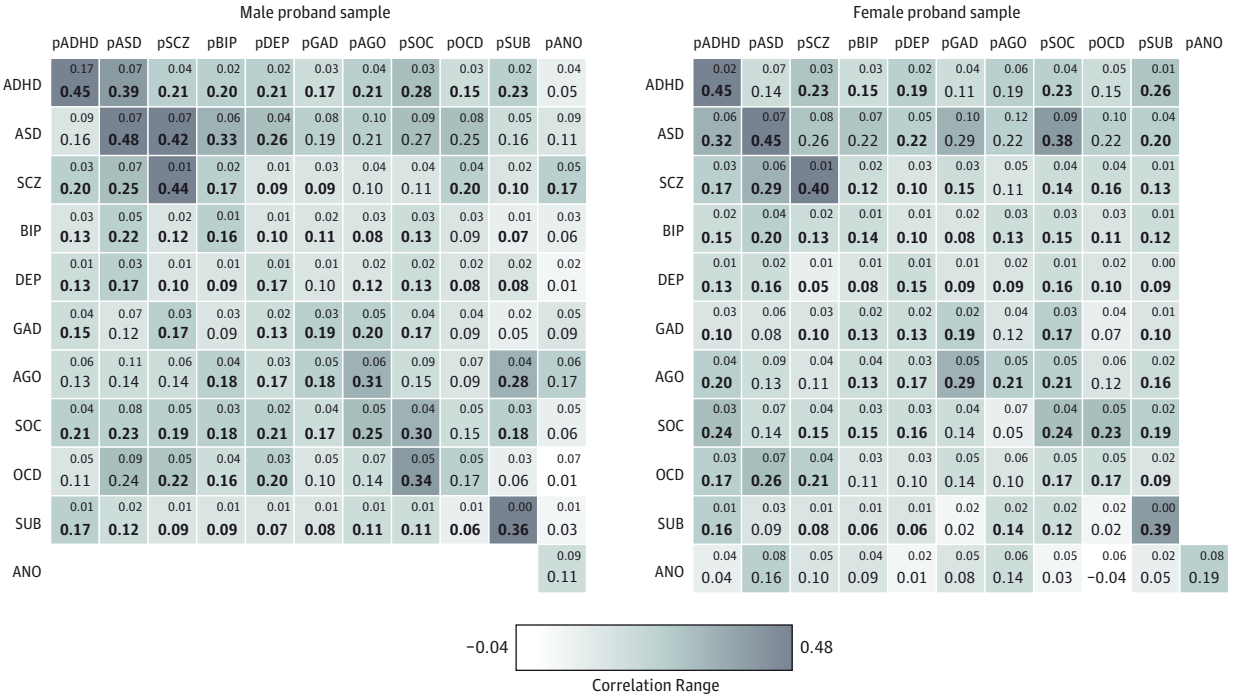
Figure 1. Within-Disorder and Cross-Disorder Partner Correlations, by Psychiatric Proband Sex, in Restricted Case Samples



The magnitude of the spousal correlations is reflected in the figure's coloration, with darker boxes indicating stronger correlations between the diagnostic status of the relevant proband (indicated by row labels) and the corresponding diagnostic status of his or her mate (indicated by column labels). pXXX is the opposite-sex partner of a proband with diagnosis XXX. Large figures in each box reflect the correlation for that row or column, with small figures indicating the standard error. Large figures in bold indicate that the correlation is statistically significant ($P < .001$). Due to unique matched populations and the possibility of multiple pairings per individual, within-disorder correlations may be asymmetric for the same comparison depending on the proband sex. Empty values in ANO and pANO rows and columns reflect confinement of analyses to female probands or partners. ADHD indicates attention-deficit/hyperactivity disorder; AGO, agoraphobia; ANO, anorexia nervosa; ASD, autism spectrum disorder; BIP, bipolar disorder; DEP, major depressive disorder; GAD, generalized anxiety disorder; OCD, obsessive-compulsive disorder; SCZ, schizophrenia; SOC, social phobia; and SUB, substance abuse.

For example, if matching for a man with ADHD, controls were selected from all male individuals who did not have an ADHD diagnosis. No further restrictions were placed to allow for representative comparison populations.

Statistical Analysis

The statistical analysis was conducted using a software program (Stata, release 13; StataCorp LP).[26] Analyses were performed by disorder, with tests repeated in each disorder-specific population (eg, ADHD cases and their matched population controls). Individuals were permitted to mate more than once, with matched controls selected anew for each separate pairing and treated as independent in the analysis. Where relevant, the software program's survey routines were used to account for the matching, with reported standard errors robust to this structure. To permit testing of sex-specific effects and to avert duplication of affected pairs, all analyses were conducted by sex.

The proportions of mated pairs in each full case and matched control sample were first summarized. Using the mated subsets, tetrachoric correlations—run first within and subsequently across disorders—were then used to evaluate the magnitude and significance of the relationship between mates' diagnostic status. Simple or conditional (cross-disorder relationships only) logistic regressions followed to illustrate the odds of each diagnosis in the mates of cases relative to the odds among the mates of matched population controls. A final analysis then merged all of these populations by ID into a single data set to (1) test the relative effect of any diagnosis (in a proband) on the odds of any diagnosis in mates and (2) explore the relationship between the number of comorbidities (in a case proband) and the presence of any psychiatric diagnoses in mates.

Due to the possible confounding effects of certain comorbidities and in an effort to isolate the mating profile of the disorder of interest, pairs were omitted from conditional analyses if (1) cases had the outcome diagnosis of interest or (2) mates had the predictor diagnosis of interest. Therefore, if examining the odds of ADHD cases selecting mates with OCD, the restricted sample would exclude pairs in which case probands had a diagnosis of OCD or mates had a diagnosis of ADHD. **Figures 1**, **2**, **3**, and **4** reflect the results of these restricted analyses. Where reported, significance was set at $P < .001$.

Results

Case Samples

The initial size of each disorder-specific sample and the proportion of these cases that mated is provided in **Table 1** and

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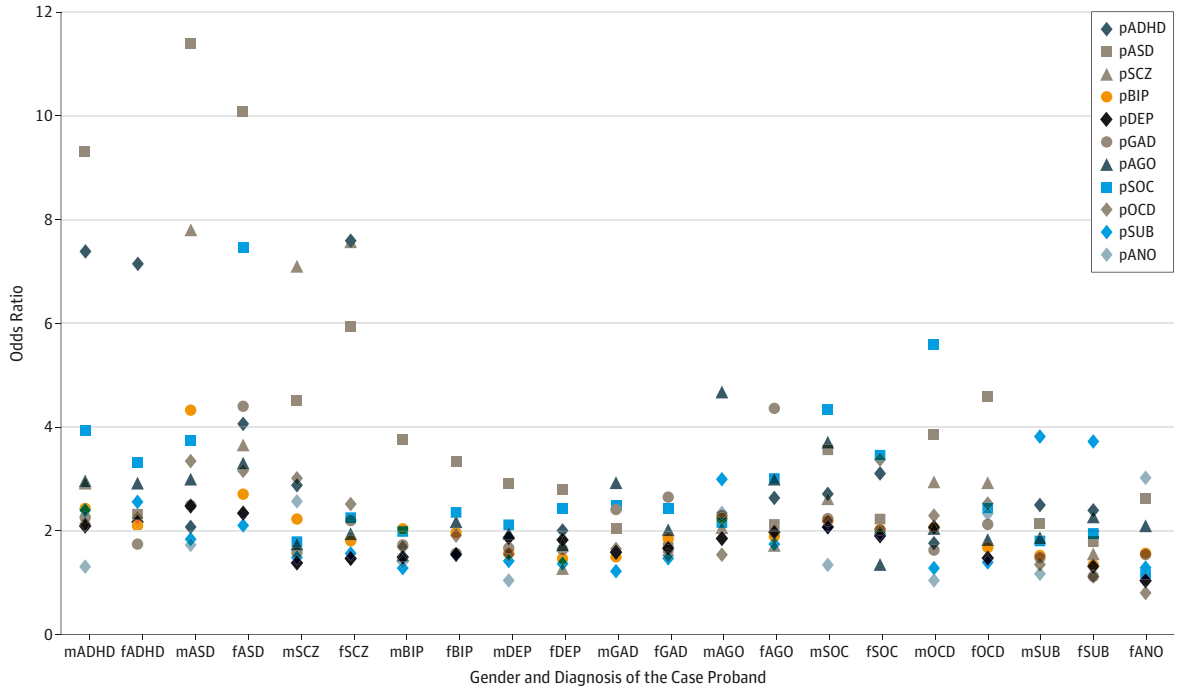
Figure 2. Dot Plot of Odds Ratios Illustrating Mating Patterns Within and Across Major Mental Disorders, by Psychiatric Proband Sex



Plotted points illustrate the increased odds, relative to matched populations, of each individual diagnosis among the opposite-sex partners of case probands (whose sex and diagnosis are labeled on the x-axis). mXXX is a male proband with diagnosis XXX, fXXX is a female proband with diagnosis XXX, and pXXX is the opposite-sex partner of a proband with diagnosis XXX. ADHD indicates attention-deficit/hyperactivity disorder; AGO, agoraphobia; ANO, anorexia nervosa; ASD, autism spectrum disorder; BIP, bipolar disorder; DEP, major depressive disorder; GAD, generalized anxiety disorder; OCD, obsessive-compulsive disorder; SCZ, schizophrenia; SOC, social phobia; and SUB, substance abuse.

Table 2. Across all samples, case probands showed significantly reduced odds of mating relative to their matched populations. The magnitude of these reductions varied by disorder and sex, with particularly attenuated rates observed among individuals with schizophrenia. Low rates of mating in ADHD, ASD, and tic disorder reflect, in part, the youth of these populations, with a respective 21.5%, 22.3%, and 19.6% of these indexes being younger than 20 years (≤2.5% for all other samples). Due to an insufficient number of paired cases, one disorder group (tic syndrome) was omitted from further analysis, while the low number of men with anorexia nervosa led to the consideration of mating patterns only among women.

Mating Patterns

Within each disorder sample (eg, ADHD case and control probands), the mates of both sexes were meaningfully correlated for diagnostic status (range, 0.11-0.48) (Figure 1). Cross-disorder correlations (range, 0.01-0.42) were also evident, being typically lower than within-disorder correlations. Patterns of these correlations varied for each disorder sample, although some clustering of pronounced interdisorder correlations was observed for the neurodevelopmental conditions (eg, ASD and ADHD) and, to a lesser extent, the anxiety disorders.

As shown in Figure 2, a disorder in a case was typically associated with a 2-fold to 3-fold increase in his or her mate's odds of having the same or an alternate condition. These risks were compounded in select conditions, such as ADHD, ASD, and schizophrenia, although small samples for some analytic combinations, particularly ASD, require cautious interpretation (the 95% CIs are shown in eFigures 1 through 11 in the Supplement).

An analysis considering the odds of any diagnosis among the mates of case probands found a significant increase for both male cases (odds ratio [OR], 2.24; 95% CI, 2.21-2.27; $P < .001$) and female cases (OR, 2.11; 95% CI, 2.08-2.14; $P < .001$). The proportion of case probands having an affected mate increased linearly with the number of comorbidities in the proband (Figure 3).

Nonpsychiatric Conditions

In contrast to psychiatric samples, mating rates were consistently high among both men and women with nonpsychiatric diagnoses (eTable in the Supplement). Meaningful spousal correlations within and across these conditions were rare (correlation range, −0.03 to 0.17) (Figure 4), with the presence of a nonpsychiatric condition in one spouse associated with little increase in his or her spouse's risk for the same or any other diagnoses (eFigure 12 in the Supplement). Of the 5 nonpsychiatric conditions, only multiple sclerosis showed a spousal correlation comparable to that observed in the psychiatric samples.

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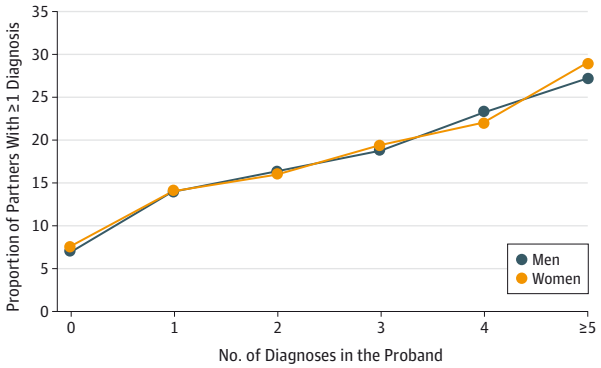
Figure 3. Linear Plot Depicting the Relationship of Psychiatric Proband Diagnosis (Total No.) to the Proportion of Partners With a Diagnosis



The proportion of case probands having an affected mate increased linearly with the number of comorbidities in the proband.

Figure 4. Within-Disorder and Cross-Disorder Partner Correlations, by Nonpsychiatric Proband Sex, in Restricted Case Samples

Male proband sample

	pCD	pDM1	pDM2	pMS	pRA
CD	0.03 −0.02	0.02 0.03	0.01 0.03	0.03 0.04	0.02 0.01
DM1	0.01 0.01	0.01 **0.08**	0.01 0.03	0.01 0.01	0.01 **0.01**
DM2	0.01 0.01	0.01 0.02	0.00 **0.09**	0.01 0.02	0.00 **0.02**
MS	0.04 0.01	0.02 −0.01	0.02 0.00	0.03 **0.14**	0.02 **0.04**
RA	0.02 0.02	0.01 0.01	0.01 0.02	0.02 0.00	0.01 **0.04**

Female proband sample

	pCD	pDM1	pDM2	pMS	pRA
CD	0.03 −0.03	0.01 0.01	0.01 0.04	0.04 0.02	0.02 0.01
DM1	0.01 0.02	0.01 **0.07**	0.01 0.02	0.02 −0.01	0.01 0.00
DM2	0.01 0.00	0.01 0.01	0.00 **0.06**	0.01 −0.03	0.01 0.01
MS	0.03 0.00	0.01 0.01	0.01 **0.04**	0.03 **0.17**	0.02 0.02
RA	0.01 0.01	0.01 0.02	0.00 **0.02**	0.02 **0.03**	0.01 **0.03**

The magnitude of the spousal correlations is reflected in the figure's coloration, with darker boxes indicating stronger correlations between the diagnostic status of the relevant proband (indicated by row labels) and the corresponding diagnostic status of his or her mate (indicated by column labels). pXXX is the opposite-sex partner of a proband with diagnosis XXX. Large figures in each box reflect the correlation for that row or column, with small figures indicating the standard error. Large figures in bold indicate that the correlation is statistically significant ($P < .001$). Due to unique matched populations and the possibility of multiple pairings per individual, within-disorder correlations may be asymmetric for the same comparison depending on the proband sex. CD indicates Crohn's disease; DM1, type I diabetes mellitus; DM2, type 2 diabetes mellitus; MS, multiple sclerosis; and RA, rheumatoid arthritis.

Discussion

This study aimed to describe patterns of mating in a broad range of psychiatric disorders using a large population-based cohort. Our results, which extend previous work in this area, indicate that (1) nonrandom mating is often present in psychiatric patients, (2) this mating exists both within and across conditions, (3) there is substantial variation in the pattern according to diagnosis, and (4) this phenomenon is not observed to the same degree in nonpsychiatric conditions.

In psychiatric samples, disorders exhibiting more marked spousal correlations and risk increases tended to be those that either emerge at an early age (eg, ADHD and ASD) or are associated with especially severe symptoms (eg, schizophrenia and substance abuse). These populations generally showed higher within-disorder correlations, with some also exhibiting marked cross-disorder correlations (eg, ADHD with ASD). Notably, some of these disorders (schizophrenia and ASD) are among those most likely to reduce overall reproductive success,[19] suggesting that these phenotypes (and, by extension, genotypes) may be under strong negative selection in the general population while being positively selected for within certain psychiatric populations. This result is an important finding given its potential implication for the maintenance of these conditions in the general population, with the possibility raised that these mating patterns compensate, to some degree, for the reductions in fecundity observed in these same mental disorders.[19]

Mating patterns varied by condition, with most psychiatric samples characterized by modest correlations across the range of disorders, while a few showed marked relationships within a select set of conditions. These spousal correlations were often higher than those observed elsewhere for traits like personality (approximately 0.10) or height and weight (approximately 0.20).[13,14,27,28] Disorders exhibiting the former, low-variance pattern included the mood disorders (eg, MDD and bipolar disorder) and select anxiety disorders (eg, GAD). Such a profile could account for the conflicting findings of prior resemblance studies[1,9,29,30] in the affective and anxiety disorders, which have rarely had the large-scale data necessary to draw out these more subtle relationships. The few multidisorder studies[9,10] that have considered resemblance for similar patient groups have found comparable correlations, generally ranging between 0.1 and 0.3. In a meta-analysis[31] considering spousal resemblance for MDD, an OR of 2.38 was reported, which is slightly higher than our estimate of approximately 1.80.

The general absence of these patterns in nonpsychiatric conditions is noteworthy, particularly given the variation of the examined conditions in terms of typical onset, course, and symptoms. The rates of mating success observed in these populations, even for early-onset conditions with behavioral symptoms (eg, type 1 diabetes mellitus), suggest clear differences between psychiatric and nonpsychiatric conditions in regard to an affected individual's mating success and selection.

Implications for Psychiatric Genetics Research

To the extent that phenotype reflects genotype, nonrandom mating of individuals who share a psychiatric disorder will result in mates who have a nonrandom distribution of the genetic variants associated with that condition. Given that a family history positive for a psychiatric disorder (eg, schizophrenia) has been associated with increased polygenic risk scores in subsequent generations,[32] it seems reasonable to anticipate a meaningful increase in genetic variance among the offspring of these dual-diagnosis pairs. Work in population genetics suggests that such an increase would be specific to additive genetic variance, with this increase aggregating over generations in the continued presence of nonrandom mating until

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Table 1. Odds of Case Probands Mating, Relative to Matched Population Probands, by Diagnosis and Gender

	All Men							
	Total Proband, No.		Proportion Mated					
Proband diagnosis	Case	Matched Population	Case, No.	%	Matched Population, No.	%	OR[a]	(95% CI)
ADHD	41 157	205 784	6383	15.5	34 413	16.7	0.92	(0.90-0.93)
ASD	18 052	90 260	880	4.9	16 766	18.6	0.22	(0.21-0.24)
Schizophrenia	37 019	185 095	9632	26.0	147 253	79.6	0.09	(0.09-0.09)
Bipolar	30 438	152 190	19 775	65.0	118 788	78.1	0.52	(0.51-0.53)
Depression	132 640	663 199	88 746	66.9	475 133	71.6	0.80	(0.79-0.81)
GAD	9984	49 920	5784	57.9	33 387	66.9	0.68	(0.66-0.71)
Agoraphobia	3557	17 785	1863	52.4	10 623	58.7	0.74	(0.70-0.79)
Social phobia	8528	42 640	3230	37.9	22 623	53.1	0.54	(0.52-0.56)
OCD	8778	43 890	2570	29.3	20 489	46.7	0.47	(0.45-0.49)
Substance	266 680	1 333 400	173 810	65.2	1 000 606	75.0	0.62	(0.62-0.63)
Anorexia	2759	13 795	614	22.3	3945	28.6	0.71	(0.65-0.78)
Tics	3628	18 140	464	12.8	3346	18.4	0.65	(0.60-0.70)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; GAD, generalized anxiety disorder; OCD, obsessive compulsive disorder; OR, odds ratio.

[a] *P* value < .001.

Table 2. Odds of Case Probands Mating, Relative to Matched Population Probands, by Diagnosis and Gender

	All Women							
	Total Proband, No.		Proportion Mated					
Proband diagnosis	Case	Matched Population	Case, No.	%	Matched Population, No.	%	OR[a]	(95% CI)
ADHD	19 502	97 510	6167	31.6	31 775	32.6	0.96	(0.94-0.98)
ASD	8044	40 220	975	12.1	11 056	27.5	0.36	(0.34-0.39)
Schizophrenia	33 562	167 810	17 236	51.4	140 203	83.6	0.21	(0.20-0.21)
Bipolar	46 381	231 905	33 977	73.3	186 325	80.4	0.67	(0.66-0.68)
Depression	212 670	1 063 350	156 683	73.7	796 813	74.9	0.93	(0.93-0.94)
GAD	18 540	92 700	13 280	71.6	68 477	73.9	0.89	(0.87-0.92)
Agoraphobia	5720	28 600	3849	67.3	19 603	68.5	0.94	(0.90-0.99)
Social phobia	9250	46 250	4790	51.8	26 629	57.6	0.79	(0.76-0.82)
OCD	11 319	56 595	5249	46.4	31 289	55.3	0.70	(0.68-0.72)
Substance	117 870	589 350	81 815	69.4	418 505	71.0	0.93	(0.92-0.94)
Anorexia	13 976	69 880	5018	35.9	30 967	44.3	0.70	(0.68-0.73)
Tics	1125	5625	339	30.1	2034	36.2	0.76	(0.69-0.84)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; GAD, generalized anxiety disorder; OCD, obsessive compulsive disorder; OR, odds ratio.

[a] *P* value < .001.

equilibrium is reached.[33] While this finding does not imply a determinant risk in a given child, at the population level, this tendency toward spousal concordance will result in a subpopulation of offspring who differ substantially from the genetic mean and are, as a whole, at heightened genetic risk for psychiatric disorders.

Most case samples also demonstrated cross-disorder mating. The genetic implications of this mating will differ depending on the degree to which these conditions stem from shared genetic risks. For instance, substance use disorders have been proposed to have largely unique genetic risk factors.[34] In theory, this hypothesis would mean that the pairing of an individual with substance abuse to an individual with a different psychiatric condition would result only in a phenotypic, rather than genotypic, correlation. However, this degree of genetic heterogeneity is highly unusual for psychiatric disorders. For instance, the genetic risks for MDD appear to be almost entirely shared by those for GAD, while the risks for both ADHD and bipolar disorder are shared to a meaningful degree with schizophrenia.[15-17,35,36] Under these circumstances, the mating of individuals with different conditions would have effects similar to a within-disorder pairing, increasing the concentration of the variants shared by these disorders while also introducing unique variants associated with the individual phenotypes. Offspring from these pairings would be at increased genetic risk for both conditions as well as for other conditions that share a similar liability profile.

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Further work will be needed to quantify these risks, untangling their effects on offspring psychopathology and the maintenance of these conditions in the population. Although few, existing population-based examinations suggest that up to 67.5% of offspring from dual-schizophrenia couples and 44.2% from dual-bipolar disorder couples may develop these disorders, suggesting strong phenotypic effects from these concentrated genetic risks.[37] Cross-pairings have been associated with attenuated, albeit still increased, proportions of diagnosed offspring.[37] A longitudinal investigation capable of examining the mating mechanisms would be a valuable addition to this discussion because such genetic effects may aggregate and differentiate over time. Certainly, nonrandom mating could offer a mechanism of origin for disorder-dense pedigrees observed in the literature,[38] with polygenic risks compounding as such mating perpetuates in a family over generations (eg, due to geographical or social isolation).

Finally, spousal resemblance for psychiatric conditions has implications for genetic models, which are usually conducted under the assumption of random mating. The presence of resemblance across most conditions refutes this assumption and indicates that models should allow for the correlation of spouses to avoid potential bias in heritability estimates (eg, in twin studies, where neglect of spousal correlations may underestimate heritability). The extra additive genetic variance also has implications for genome-wide association studies and single-nucleotide polymorphism-based heritability estimates because these methods are limited to additive genetic variance.

Limitations

Our definition of mating fails to capture some alternative pairings (eg, childless, unmarried, and cohabitating partners). As the registers continue to develop, better capture of these relationships may be anticipated. Furthermore, reliance on register diagnoses inherently limits our examination to individuals who have sought outpatient or inpatient care for psychiatric concerns, with such populations potentially constituting a unique subset of the whole affected population. While it is difficult to quantify the impacts of this detection bias, it may be noted that we have found largely comparable results for disorders that frequently require inpatient admissions and are thus well captured in the registers (eg, schizophrenia and bipolar disorder) and those that are typically managed in outpatient settings and may therefore be more variably captured (eg, MDD and GAD). In addition, the magnitude of the relationships observed in our samples accord, to a large degree, with prior research conducted in related populations sampled using different approaches.[9,10]

We are also limited in the comment we can offer on the mechanisms underlying the mating patterns observed (eg, assortative mating vs marital interaction). Certainly, it is possible that the presence of a disordered behavior in one spouse (eg, alcohol dependence) could influence his or her mate's consumption (interaction) or spur the development of an alternative condition (eg, MDD) as a reaction (contagion). Individuals with an affected mate may also be more likely to access services and receive their own diagnosis (detection bias). This being said, prior work has failed to find a relationship between marriage duration and either the magnitude of resemblance or the rates of spousal concordance for psychiatric conditions.[9,10] Furthermore, the negligible shared environment effects observed in many heritable psychiatric conditions would favor the phenotypic assortment alternative.[6] Moreover, our finding of marked resemblance for neurodevelopmental conditions suggests a role for assortment in at least some populations because these conditions would be present over the life span.

Finally, while the samples used in this investigation are degrees of magnitude larger than those of prior investigations, low rates of mating in some case populations (most notably ASD) require conservative interpretation. Studies offering further coverage of these populations would be a valuable addition to this area of inquiry. Given the relationship observed in our samples between the number of comorbidities and the risk of nonrandom mating, work exploring the role of comorbidity in this phenomenon would also be of interest.

Conclusions

This work suggests that nonrandom mating is widespread in psychiatric populations both within and across the spectrum of psychiatric disorders. This phenomenon, which is not observed in nonpsychiatric populations, may hold important implications for how we understand the familial transmission of these conditions and the ubiquity of comorbidity and complex symptoms in clinical populations. Furthermore, the results challenge a fundamental assumption of current genetic research methods, suggesting that more attention to this issue is warranted.

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Study concept and design: Nordsletten, Larsson, Lichtenstein, Mataix-Cols.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Nordsletten, Crowley.
Critical revision of the manuscript for important intellectual content: Larsson, Crowley, Almqvist, Lichtenstein, Mataix-Cols.
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collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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