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ORIGINAL ARTICLE

Fecundity of Patients With Schizophrenia, Autism, Bipolar Disorder, Depression, Anorexia Nervosa, or Substance Abuse vs Their Unaffected Siblings

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Context: It is unknown how genetic variants conferring liability to psychiatric disorders survive in the population despite strong negative selection. However, this is key to understanding their etiology and designing studies to identify risk variants.

Objectives: To examine the reproductive fitness of patients with schizophrenia and other psychiatric disorders vs their unaffected siblings and to evaluate the level of selection on causal genetic variants.

Design: We measured the fecundity of patients with schizophrenia, autism, bipolar disorder, depression, anorexia nervosa, or substance abuse and their unaffected siblings compared with the general population.

Setting: Population databases in Sweden, including the Multi-Generation Register and the Swedish Hospital Discharge Register.

Participants: In total, 2.3 million individuals among the 1950 to 1970 birth cohort in Sweden.

Main Outcome Measures: Fertility ratio (FR), reflecting the mean number of children compared with that of the general population, accounting for age, sex, family size, and affected status.

Results: Except for women with depression, affected patients had significantly fewer children (FR range for those with psychiatric disorder, 0.23-0.93; $P<10^{-10}$). This reduction was consistently greater among men than women, suggesting that male fitness was particularly sensitive. Although sisters of patients with schizophrenia and bipolar disorder had increased fecundity (FR range, 1.02-1.03; $P<.01$), this was too small on its own to counterbalance the reduced fitness of affected patients. Brothers of patients with schizophrenia and autism showed reduced fecundity (FR range, 0.94-0.97; $P<.001$). Siblings of patients with depression and substance abuse had significantly increased fecundity (FR range, 1.01-1.05; $P<10^{-10}$). In the case of depression, this more than compensated for the lower fecundity of affected individuals.

Conclusions: Our results suggest that strong selection exists against schizophrenia, autism, and anorexia nervosa and that these variants may be maintained by new mutations or an as-yet unknown mechanism. Bipolar disorder did not seem to be under strong negative selection. Vulnerability to depression, and perhaps substance abuse, may be preserved by balancing selection, suggesting the involvement of common genetic variants in ways that depend on other genes and on environment.

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PSYCHIATRIC DISORDERS HAVE long puzzled researchers by defying the expectations of natural selection.[1] From an evolutionary viewpoint, selection should remove genetic variants that reduce an individual's ability to reproduce ("fitness") because they will produce fewer offspring to inherit those variants. However, psychiatric disorders do not fit this model. They combine substantial heritability with moderate to high prevalence, early age at onset, and reduction in fitness compared with the general population. Several hypotheses have been put forward on how psychiatric disorders survive in the population,[2-5] but the mechanisms that maintain the genetic variants conferring susceptibility to these disorders remain unclear.

Insights into the form of selection pressure on psychiatric disorders may help direct research toward identifying specific causal pathways. The large disparity between heritability estimates from family studies and the amount of variance in psychiatric disorders explained by identified risk alleles has become known as the "missing heritability."[6] Current genome-wide association studies are based on the

common disorder–common variants hypothesis, which presumes that many low-risk high-frequency alleles directly lead to highly prevalent complex disorders. Evidence suggesting an alternative reason why risk alleles remain in the population could explain why more causal variants have not been discovered through linkage or association studies.

Several alternatives to the common disorder–common variants hypothesis exist. Autism, bipolar disorder, and schizophrenia have been associated with increased paternal age.[7-10] Older paternal age carries a risk of an increased number of de novo mutations during spermatogenesis,[11] which in turn may lead to deleterious phenotypes in the next generation.[12] Alternatively, deleterious genes that exist in the population may only recently have come under purifying selection, as changes in selection pressures have made them detrimental in the present environment. A competing hypothesis is that causal genetic variants may not be entirely deleterious but may also confer benefits (eg, creativity[13]) and that balancing selection maintains these variants in the population at optimal frequency. Possible mechanisms for balancing selection include heterozygote advantage, pleiotropic antagonism, and gene-environment interactions. A specific form of balancing selection is sexual antagonism, where a trait may be beneficial to one sex but harmful to the other.

To our knowledge, this analysis is the first to evaluate the fecundity of affected individuals and their siblings for multiple psychiatric disorders, including schizophrenia, autism, bipolar disorder, depression, anorexia nervosa, and substance abuse. Previous research has focused solely on psychosis, and a recent meta-analysis[14] found no overall increase in the fecundity among siblings of those with schizophrenia. Similar evidence is missing for most other psychiatric disorders. The aim of this study was to examine sibling fecundity to evaluate evidence for the aforementioned theories for the continued prevalence of psychiatric disorders (**Table 1**). Under balancing selection, we expected that unaffected siblings of those with psychiatric disorders would enjoy increased reproductive fitness because they would benefit from the positive effects of the same genetic variants that contributed to psychiatric disorders in their kin. Sex-specific effects on sibling fecundity may provide evidence for sexual antagonism, with the same genetic variants benefiting one sex at the cost of the other. For de novo or recent highly penetrant mutations, no reduction in the fecundity would be expected in unaffected siblings (as long as affected siblings are diagnosed). If these disorders were affected by multiple variants that were ancestrally neutral but deleterious in today's environment, we expected to see decreased fecundity in siblings due to an increased probability of sharing those variants and the unsuited environment.

Table 1. Hypotheses of Maintenance of Genes for Psychiatric Disorders and Predicted Results for Fecundity in Affected Individuals and Their Unaffected Siblings

	Predicted Result for Fecundity	
Hypothesis	Affected Individuals	Unaffected Siblings
Balancing selection	Decreased	Increased in proportion to the decrease in affected individuals
Sex-dependent selection	Decreased to a greater extent in one sex	Decreased in the same sex as that of affected individuals but increased in the opposite sex
De novo mutation	Greatly decreased	No change
Ancestral neutrality	Decreased	Decreased to a lesser extent owing to shared genes and environment

METHODS

POPULATION DATABASES

The data set was drawn from the Multi-Generation Register, which includes children born in Sweden since 1932 and their biological parents.[15] All individuals alive in 1960 and all births from this point onward were recorded in the register. Paternity is assumed to be the husband of the mother at the time of birth or "by acknowledgment" for unwed mothers. This data set was linked to the Swedish Hospital Discharge Register, which covers virtually all psychiatric hospitalizations since 1973 in Sweden[16] and has been previously validated.[17,18] It also includes partial coverage of outpatient diagnoses from 2001 onward. The use of this database has been approved by the ethics committee at the Karolinska Institutet, Stockholm, Sweden. Diagnoses were established according to the *International Classification of Diseases* (*ICD*), *Eighth Revision* (1973-1987), *Ninth Revision* (1987-1996), and *Tenth Revision* (1996 onward). These registers were linked using an individual's unique national registration number. The analyses were restricted to 2 356 598 individuals born in Sweden between 1950 and 1970, for whom most of their adult life was covered in the Swedish Hospital Discharge Register and who would have completed most of their reproductive life span (age 40 years for the youngest individuals). Only individuals for whom both parents were known were included in the birth cohort, although this limitation was not applicable when calculating the number of offspring.

DISORDERS CLASSIFICATION

Six disorders were examined, including schizophrenia, autism, bipolar disorder, depression, anorexia nervosa, and substance abuse (including alcohol use disorder). The 6 disorders were chosen to differ in terms of prevalence, severity, heritability, and their distribution between men and women. In all cases, previous studies[19-24] using the Multi-Generation Register and the Swedish Hospital Discharge Register were used as a basis for the selection of *ICD* codes. Following the validation of bipolar disorder in the Swedish Hospital Discharge Register by Sellgren et al,[24] 2 or more diagnoses over a lifetime were required o be included. For all other disorders, only a single lifetime diagnosis in the Swedish Hospital Discharge Register was required. Svensson et al[23] had previously examined schizophrenia in the Multi-Generation Register and the Swedish Hospital Discharge Register in an earlier (nonoverlapping) birth cohort. Schizophrenia was defined by 1 or more recorded diagnoses of code 295 in *ICD-8* and *ICD-9* and by codes F20, F23.1, F23.2, and F25 in *ICD-10*. Autism was defined by code 299.0 in *ICD-9* and by codes F84.0, F84.1, F84.5, and F84.9 in *ICD-10* and was not defined in *ICD-8*. Bipolar disorder was defined by code 296 (excluding code 296.2) in *ICD-8*, by code 296 (excluding code 296.1) in *ICD-9*, and by codes F30 and F31 in

Table 2. Epidemiological Details for 6 Psychiatric Disorders Among the Cohort of 2 356 598 Individuals Born in Sweden Between 1950 and 1970

Psychiatric Disorder	No. of Affected Individuals	Prevalence, %	Female-Male Ratio	No. of Children Among the Cohort, Mean No. of Affected	No. of Unaffected Siblings
Schizophrenia	18 890	0.80	1:1.5	0.61	28 644
Autism	2947	0.12	1:2	0.56	4471
Bipolar disorder	14 439	0.61	1.5:1	1.48	22 986
Depression	81 295	3.44	1.4:1	1.78	119 645
Anorexia nervosa	3275	0.14	10.4:1	1.46	5172
Substance abuse	55 933	2.37	1:2.3	1.49	81 592

ICD-10. One of these was allowed to be code 296.2 in *ICD-8* or code 296.1 in *ICD-9*. Depression was defined by codes 296.0, 296.2, and 298.0 in *ICD-8*; by codes 296.2, 296.3, and 298.0 in *ICD-9*; and by codes F32 and F33 in *ICD-10*. Anorexia nervosa was defined by code 306.5 in *ICD-8*, by code 307.1 in *ICD-9*, and by code F50.0 in *ICD-10*. Last, substance abuse was defined by codes 303 and 304 in *ICD-8*; by codes 303, 304, 305.1, and 305.9 in *ICD-9*; and by codes F10 through F19 (excluding subsection 0.5, diagnosing substance abuse with psychosis) in *ICD-10*. Diagnoses were made on discharge by the treating physician. No hierarchical diagnostic practice was used; hence, individuals with comorbidity could appear in more than 1 category. A large amount of comorbidity existed within the sample, with affected individuals being diagnosed as having at least 1 other disorder in 45.7% of individuals with schizophrenia, 48.9% with autism, 71.7% with bipolar disorder, 26.4% with depression, 26.8% with anorexia nervosa, and 30.0% with substance abuse. High levels of comorbidity between psychiatric disorders is a common feature of cohort studies and has been described at length elsewhere.[25] For the objectives of this study, we first analyzed each disorder separately without accounting for comorbidities. A secondary analysis was then performed that corrected for comorbidities by analyzing all disorders simultaneously. Family identification codes were used to identify unaffected full siblings, while affected siblings were considered affected individuals, not siblings. The results for our identification of affected individuals and their siblings are summarized in **Table 2**.

MEASURE OF FECUNDITY

Data were analyzed using generalized estimating equations,[26,27] accounting for similarity in the number of children within families. To measure the reproductive fitness of each group, a fertility ratio (FR) was calculated based on the number of children individuals in that group had compared with the general population, correcting for the year of birth. For example, if the disease group had an FR of 0.5, it meant they had on average half as many children as the general population, while an FR of 2 meant they had twice as many. To permit testing for sex-specific effects and to avoid confounding by age differences at parenthood and the mean number of children, we compared affected men with the general population of men, and the same for affected women. Similarly, siblings of affected individuals were compared with only those in the general population of the same sex, with the additional requirement that they had at least 1 sibling, to account for any bias resulting from being a sibling. Socioeconomic effects have been shown to influence the risk for psychiatric disorders[28] and could potentially confound our analysis. To account for socioeconomic status, we corrected for both paternal and maternal education levels derived from the 1970 census data.[29] Parental education level rather than the self-education level was used to avoid reverse causation. Data on at least 1 parent were available for more than 95% of individuals.

To interpret the FRs of affected individuals and their siblings together, we followed the method by Haukka et al[30] and compared the prevalence of affected individuals and siblings plus that of their combined children. Therefore, we combined the estimated number of children from affected individuals and their siblings, and we then divided that sum by the estimated total number of children for the entire 1950 to 1970 birth cohort. The total estimated number of children was derived from the FR of each group (affected, sibling, and remaining population), multiplied by the mean number of children, and weighted for by each group's frequency in the birth cohort. Using the FR rather than the actual number of children of each individual, we corrected for the year of birth and the unequal distribution of affected individuals born each year. For this analysis, we used the FRs that were not corrected for comorbidities. All the analyses were performed using commercially available software (STATA, release 12; StataCorp LP).[31]

RESULTS

The mean (SD) number of children for the birth cohort was 1.76 (1.27). Paternal and maternal education levels were found to be significantly associated with fecundity. Because only minor differences were observed between the adjusted and nonadjusted estimates, only the adjusted estimates are presented herein. The mean (SD) number of siblings for the birth cohort was 1.68 (1.38).

SCHIZOPHRENIA

Individuals with schizophrenia had fewer children compared with the general population, with FRs of 0.23 (95% CI, 0.23-0.24; $P < 10^{-10}$) for men and 0.47 (95% CI, 0.46-0.48; $P < 10^{-10}$) for women (**Figure 1**). Sisters of affected individuals had a significantly increased number of children (FR, 1.02; 95% CI, 1.01-1.03; $P = .01$), while brothers of affected individuals showed significantly decreased fecundity (FR, 0.97; 95% CI, 0.96-0.99; $P < .001$) (**Figure 2**). When comorbidities were included in the analysis, the increased fecundity in sisters disappeared.

AUTISM

Individuals with autism had significantly fewer children, in men (FR, 0.25; 95% CI, 0.23-27; $P < 10^{-10}$) and women (FR, 0.48; 95% CI, 0.44-0.51; $P < 10^{-10}$). Brothers of affected individuals also had fewer children (FR, 0.94; 95%

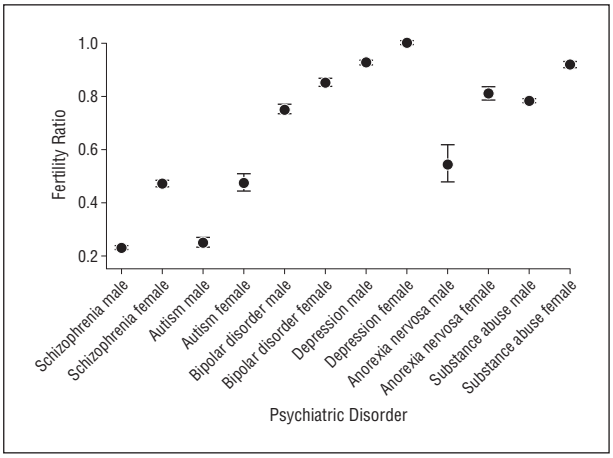

Figure 1. Fertility ratios for individuals with schizophrenia, autism, bipolar disorder, depression, anorexia nervosa, and substance abuse. A fertility ratio of 1 (highlighted) represents that of the general population.

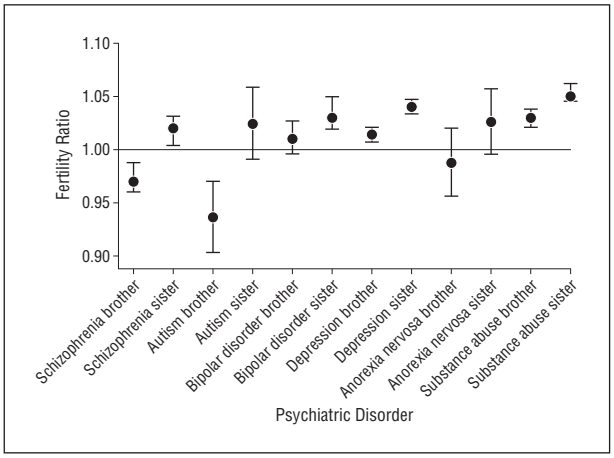

Figure 2. Fertility ratios for unaffected siblings of individuals with schizophrenia, autism, bipolar disorder, depression, anorexia nervosa, and substance abuse. A fertility ratio of 1 (highlighted) represents that of the general population.

CI, 0.90-0.97; $P < .001$), while sisters of affected individuals showed no significant difference from the general population. These results did not differ significantly when comorbidities were included in the analysis.

BIPOLAR DISORDER

Men and women with bipolar disorder had fewer children than the general population (male FR, 0.75; 95% CI, 0.73-0.77; $P < 10^{-10}$; female FR, 0.85; 95% CI, 0.84-0.87; $P < 10^{-10}$). Brothers of affected individuals showed no significant difference from the general population, while sisters of affected individuals had an increased number of children (FR, 1.03; 95% CI, 1.02-1.05; $P < 10^{-5}$). When correcting for comorbidity, the increased fecundity in sisters disappeared, and the reduced fecundity in affected individuals increased to just below that of the general population (male FR, 0.94; 95% CI, 0.92-0.96; $P < .001$; female FR, 0.95; 95% CI, 0.93-0.97; $P < .001$).

DEPRESSION

Men with depression had fewer children (FR, 0.93; 95% CI, 0.92-94; $P < 10^{-10}$), but women with depression showed no significant difference from the general population. Siblings of affected individuals had more children compared with the general population (brothers' FR, 1.01; 95% CI, 1.01-1.02; $P < .0001$; sisters' FR, 1.04; 95% CI, 1.03-1.05; $P < 10^{-10}$). This increased fecundity in siblings remained when comorbidities were accounted for, although the reduced number of children among affected men disappeared and the fecundity among women with depression increased (FR, 1.03; 95% CI, 1.03-1.04; $P < .001$).

ANOREXIA NERVOSA

Individuals with anorexia nervosa showed a reduced number of children in men (FR, 0.54; 95% CI, 0.48-62; $P < 10^{-10}$) and in women (FR, 0.81; 95% CI, 0.79-84; $P < 10^{-10}$). Neither the fecundity of brothers nor sisters differed from that of the general population. These results did not change after correction for comorbidities.

SUBSTANCE ABUSE

Men having a diagnosis of substance abuse had significantly fewer children than the general population (FR, 0.78; 95% CI, 0.78-79; $P < 10^{-10}$), as did women having a diagnosis of substance abuse (FR, 0.92; 95% CI, 0.91-0.93; $P < 10^{-10}$). Siblings of individuals with substance abuse had more children than the general population, with FRs of 1.03 (95% CI, 1.02-1.04; $P < .0001$) for brothers and 1.05 (95% CI, 1.05-1.06; $P < 10^{-10}$) for sisters. These values did not differ significantly when comorbidities were included.

COMMENT

To our knowledge, this is the first time the fitness of relatives has been examined for individuals with these psychiatric disorders (other than schizophrenia and bipolar disorder). Across disorders, affected men had a consistently greater reduction in fecundity than affected women. A similar sex difference was observed among siblings: sisters of individuals with psychiatric disorders had more children than their brothers. The degree of fecundity reduction in affected individuals and the associated increase in the fecundity among siblings differed by disorder, which suggests that different types of psychiatric disorders are under different selection pressures.

STUDY LIMITATIONS

Our conclusions rely on the assumption that the fecundity measured truly reflects these individuals' reproductive fitness. Ideally, the number of grandchildren rather than children would be used to measure an individual's long-term fitness, and this should become possible in the future with the continuation of the Multi-Generation Register in Sweden. The fecundity in affected individuals may be decreased by effects of medication or hospitalization, which may have distorted our findings. Voluntary and compulsory sterilizations were historically performed in Sweden until the 1970s, including targeting those with

Table 3. Fitness Calculations of the Observed Proportions of Affected Individuals in the 1950 to 1970 Birth Cohort and the Estimated Proportions of Their Affected Children in the Next Generation

Psychiatric Disorder	Proportion of Affected Individuals		
	Observed in the 1950-1970 Birth Cohort	Estimated in the Next Generation	Change, %
Schizophrenia	0.022	0.016	−25
Autism	0.003	0.002	−28
Bipolar disorder	0.012	0.011	−6
Depression	0.092	0.093	1
Anorexia nervosa	0.003	0.002	−10
Substance abuse	0.066	0.064	−3

psychiatric disorders. It should be noted that most of those sterilized were women, while our results consistently show a greater reduction in male fecundity.[32,33] Last, children of those with a psychiatric disorder may go unrecorded as a result of stigma or chaotic lifestyles (eg, emigration), leading to an artificial lowering of their fecundity. However, these concerns are not applicable to unaffected siblings. Therefore, we believe that the number of children born to siblings of individuals with psychiatric disorders accurately reflects their fitness.

Is reproductive success today representative of reproductive success in the past? Recent reductions in child mortality and in the mean number of children per adult, as well as the increased use of contraceptives, raise questions about how well evolutionary fitness can be measured in the modern world. This is important because a trait's prevalence is dependent on the selection it has encountered in previous generations, not the current one. However, several reasons indicate why we would expect fitness today to reflect fitness in previous generations to some extent. First, changes in fecundity may reflect a biological or physiological difference in fertility that affects fitness regardless of culture or setting (eg, reduced sperm count). Second, it has been argued that the inability to attract a mate is responsible for low fitness in those with psychiatric disorders (reviewed by Keller and Miller[2]), supported by evidence showing that low marriage rates mediate the effect of psychiatric disorders on fitness.[34] If this is the case, then modern improvements in contraceptives and child mortality occur after the selection against individuals with psychiatric disorders has already occurred and so have less influence. Third, the extent of the impairment experienced by those with psychiatric disorders in traditional communities is high, suggesting that the effects are not culture specific.[35,36] Although our measure was suboptimal, we maintain that the large differences in fecundity suggest as close a measure of fitness as any other available in human data sets.

Finally, the generalization of a single etiology to a disorder may be unfounded. As described in the "Methods" section, considerable comorbidity exists between disorders. Longitudinal, family, and molecular studies[25,37,38] have demonstrated that psychiatric disorders show considerable overlap and share genetic risk variants. We attempted to tackle this by analyzing performing analyses with vs without accounting for comorbidities, and this had little effect (except for bipolar disorder). More problematic is the evidence for considerable genetic and phenotypic heterogeneity within psychiatric disorders.[39] Heterogeneity within disorders means that caution must be applied to generalizations of their genetic etiology.

SEX-SPECIFIC EFFECTS

Across disorders, the fecundity of affected men was lowered more than that of affected women, a finding that had been noted in previous studies.[14,40] This sex-specific effect suggests that psychiatric morbidity impairs interest or ability to find suitable mating partners or inhibits biological fertility to a greater extent in men. Several hypotheses attempt to explain why. Evolutionary theory suggests that male species have the potential for greater variance in reproductive success than female species.[41] This is assumed to result from their minimal investment being cheap compared with the minimal investment of women (ie, the cost of sperm production compared with 9 months of pregnancy). Because of this underlying difference in investment, it benefits women to be more selective in their choices of a mate. This can lead to mating systems often seen in mammals where "dominant" males have multiple mates, while others have none. Because of the greater variability in male fitness and the pressure on females to be selective, a genetic or environmental burden can have an exaggerated effect on a male's ability to find a mate. However, it should be noted that in this data set men had a lower variance in the number of children they had compared with women. Men also had fewer children on average than women, suggesting differences in reporting. A mother must be present at the birth of a child, but paternal uncertainty can exist even when a father is named. Another hypothesis is that fathers with a psychiatric disorder may be less likely to be recorded as the child's parent. Last, male fertility may be more susceptible than female fertility to sexual adverse effects of psychiatric treatment.

SCHIZOPHRENIA

Our findings for schizophrenia suggest a decrease in the fecundity of affected individuals similar to that found in a recent meta-analysis.[14] Our results suggest a strong selection pressure to remove genetic variants associated with schizophrenia from the population (**Table 3**). This is further evidence for the role of recent or de novo mutations in the genetic susceptibility to schizophrenia that have neither reached the frequency of nor existed long enough to be removed from the population.[12,42] This could act in conjunction with common variants' having too small an effect size to experience negative selection.[38] Our analysis also found a slight increase in the fecundity among sisters of affected individuals and a decrease in the fecundity among their brothers, although the increase in the fecundity of sisters disappears after correction for comorbidities. This trend in sibling fecundity is in agreement with several previous studies.[23,30,43,44] We have 2 potential hypotheses on why this might be the case. First, owing to the high heritability of schizophrenia and its

greater prevalence and severity among men, some brothers may have mild symptoms of schizophrenia but lack this diagnosis in our database. Second, schizophrenia may be the result of sexually antagonistic genes that are beneficial to female fitness at the expense of male fitness. This would be in agreement with the observations that schizophrenia affects men more severely than women and that the effect on fitness of shared genes in siblings is dependent on sibling sex. However, this may only be a partial explanation because the benefit to sisters does not compensate for the reduction in fitness seen in the affected individuals or brothers (Table 3).

AUTISM

Individuals with autism showed the greatest reduction in fecundity among all examined disorders. This was not unexpected because previous investigations have shown that few individuals with autism ever married or had children (eg, as demonstrated in the study by Larsen and Mouridsen[45]). The pattern of fecundity in affected individuals and siblings is similar to that of schizophrenia, with a slight increase in sisters' fecundity (nonsignificant herein) and a decrease in brothers' fecundity. As discussed for schizophrenia, this may be reflective of sexually antagonistic genes or undiagnosed symptoms in brothers. Therefore, we propose that rare highly deleterious variants and sexually antagonistic polymorphisms may contribute to the genetic disposition to autism. The similarity to schizophrenia is notable because it has been proposed that the autistic and psychotic spectrums reflect 2 extremes of social cognition.[46] It is unclear whether our results reflect a similar etiology or, as suggested by Crespi and Badcock,[46] they are opposite extremes of the same trait and come under the same stabilizing selection pressure. That both disorders show evidence for sexual antagonism supports the proposal by Crespi and Badcock that they are the result of sexual conflict.

BIPOLAR DISORDER

Unlike the other highly heritable disorders, bipolar disorder showed a low reduction in fecundity among affected individuals. This was accompanied by increased fecundity among sisters of affected individuals. However, owing to the large amount of comorbidity (see the "Methods" section), when this was corrected for, the fecundity of affected individuals increased to just below that of the general population. This agrees with the results of another study[34] of affective psychosis in Sweden but disagrees with other studies.[40,47,48] These studies have differed slightly in terms of diagnostic criteria, which may explain these discrepancies. It has been suggested that the introduction of lithium as a treatment for bipolar disorder has led to improved functioning and, as a result, greater fecundity in those populations where treatment is available.[49]

DEPRESSION

Notably, depression was an exception to the 5 other studied disorders. Female depressed individuals showed no difference in fecundity compared with the general population and had a slight increase in the fecundity after correction for comorbid disorders. Male depressed individuals showed a small decrease in the fecundity, although this too disappeared after correction for comorbidities. This contradicts the estimates of reduced fertility, especially in women, obtained from clinical samples of depressed individuals[50] and in a study[40] similar in design to ours using population registers in Denmark. The *ICD* classification used herein did not include identification of postnatal depression, and it is unclear to what extent this may lead to an increase in female fertility among individuals with depression. Furthermore, siblings of both sexes showed increased fecundity, and when this was taken into account, we found no selection acting against depression (Table 3). Rather, genes associated with depression seem to be maintained in the population by balancing selection because the cost to affected individuals is roughly equal to the benefit to their siblings. If this is the case, it would be the first strong evidence for balancing selection in a psychiatric disorder. The exact mechanism by which siblings benefit is beyond the scope of our analysis and is a line of future investigation. It has been proposed by Allen and Badcock[51] that depression may be adaptive in eliciting support from others. In parallel to the unique lack of negative influence on fecundity at the population level, depression stands out as a psychiatric disorder for which direct genetic associations have been most difficult to identify.[52-55] We propose that genetic studies in depression may benefit from the exploration of genetic and environmental dependencies that may contribute to balancing selection. An alternative explanation could be that environmental factors shared by siblings are associated with both an increased risk of depression and a higher fecundity.

ANOREXIA NERVOSA

Our analysis of anorexia showed a decrease in the fecundity among affected individuals but no difference in sibling fecundity. Our estimates of FRs in anorexia (0.54 in men and 0.81 in women) were less severe than a previous estimate from a clinical sample.[56] Our calculations suggest that anorexia is under weaker negative selection relative to schizophrenia and autism (Table 3).

SUBSTANCE ABUSE

Substance abuse was associated with reduced fecundity in affected individuals, but we found evidence for significantly increased fecundity in siblings of both sexes. Our findings suggest that this increased fecundity in siblings almost entirely accounts for the cost to affected individuals, with only a slight decrease (−3%) in the frequency of these individuals' genes predicted each generation. Considering that most drugs are a new environmental exposure when seen from an evolutionary perspective, it is possible that there has been insufficient time for selection to act on risk alleles. However, some evidence in the case of alcohol metabolism indicates that selection has affected different human populations differently.[57] Because alcohol abuse is the most frequent form of substance abuse in Sweden, we can as-

sume there has been sufficient time for some selection to have occurred.[58] It has also been suggested that substance abuse is associated with risk-taking behavior in both sexes, including sexual risk taking.[59]

SUMMARY AND RELEVANCE FOR PSYCHIATRIC GENETICS

The results of our analyses have several implications for future genetic studies. It seems likely that different evolutionary mechanisms underlie the persistence of the various psychiatric disorders. This in turn suggests that their genetic architecture may differ, so it is not surprising that the search for causal variants has proved more fruitful in some disorders than in others. More specifically, it seems that genetic variants conferring liability to schizophrenia, autism, and anorexia nervosa are under strong selection to be removed from the population. The continued high prevalence of schizophrenia and autism despite this strong negative selection, in combination with the aforementioned association with increased parental age, suggests that a high rate of de novo mutations may be maintaining these disorders in the population. The possibility of sexually antagonistic genes in schizophrenia and autism suggests that studies might benefit from male-only analysis, without women, who may be unaffected by risk alleles. Bipolar disorder did not seem to be under such strong negative selection and, after correcting for comorbidities, did not show sex-specific effects or changes in sibling fecundity.

Depression and, to a lesser extent, substance abuse, seems to be maintained by genes that are beneficial under some circumstances (ie, in siblings) but detrimental in others (ie, affected individuals). This suggests that gene-environment or gene-gene interactions have a large role in these disorders, for which some supporting evidence exists in depression.[60,61] This would decrease the power of studies comparing cases and controls, where many controls might also carry the genes that are "causal" for depression but not have the necessary genetic or environmental background risk factors to develop the disorder. Genes that interact with the environment may provide not only susceptibility to negative environments but also the ability to thrive in positive environments.[60] If the beneficial aspect of these genes is opposite to the disorder itself, rather than acting on a separate phenotype, then selecting high-functioning individuals as supercontrols might even increase the frequency of causal genetic variants in the controls. However, at this stage we have no evidence why siblings of individuals with depression or substance abuse would have increased fitness, and the observation could result from shared environmental factors uncorrected for in this analysis. Overall, a focus on case-only and exposed-only studies (eg, as in the study by Caspi et al[62]) might be more successful in disentangling the genetics of these disorders.

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Correction

Errors in Figure Legend and Figure. In the Original Article titled "Development of a Computerized Adaptive Test for Depression" by Gibbons et al, published in the November issue (2012;69[11]:1104-1112), an error occurred in the legend to Figure 2 on page 1108. The last sentence of the legend should have read, "Error bars indicate the range; horizontal lines, the 10th, 50th, and 90th percentile points, respectively." An error also occurred in Figure 3 on page 1109. The figure should have illustrated that a patient with a Computerized Adaptive Test–Depression Inventory (CAT-DI) score of −0.6 would have a probability of major depressive disorder (Pr[MDD]) equal to 0.50 and that a patient with a CAT-DI score of 0.5 would have a Pr(MDD) equal to 0.97. This article was corrected online.