Severe Mental Disorders in Offspring With 2 Psychiatrically Ill Parents

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Background: Studies of couples of psychiatric patients with children allow us to calculate the effects of double predispositions on morbid risk in the offspring, which is of interest for molecular genetic research and for genetic counseling.

Objective: To determine the risks in offspring of receiving a diagnosis of schizophrenia, bipolar disorder, unipolar depressive disorder, or any diagnosis from parents who both have received a diagnosis of schizophrenia or bipolar disorder.

Design: National register-based cohort study.

Setting: Denmark.

Participants: A population-based cohort of 2.7 million persons born in Denmark, alive in 1968 or born later than 1968, with a register link to their mother and father and aged 10 years or older in 2007.

Main Outcome Measure: Risk of schizophrenia or bipolar disorder, calculated as cumulative incidences by age 52 years.

Results: The risk of schizophrenia in 270 offspring of 196 parent couples who were both admitted to a psychiatric facility with a diagnosis of schizophrenia was 27.3% (increasing to 39.2% when schizophrenia-related disorders were included) compared with 7.0% in 13 878 offspring from 8006 couples with only 1 parent ever admitted for schizophrenia and 0.86% in 2 239 551 offspring of 1 080 030 couples with neither parent ever admitted. The risk of bipolar disorder was 24.9% in 146 offspring of 83 parent couples who were ever admitted with bipolar disorder (increasing to 36.0% when unipolar depressive disorder was included) compared with 4.4% in 23 152 offspring from 11 995 couples with only 1 parent ever admitted and 0.48% in 2 239 553 offspring of 1 080 030 couples with neither parent ever admitted. Risks of schizophrenia and bipolar disorder in offspring of couples with 1 parent with schizophrenia and the other with bipolar disorder were 15.6% and 11.7%, respectively. The maximal risks of any psychiatric disorders in the offspring of parents both with schizophrenia or both with bipolar disorder were 67.5% and 44.2%, respectively.

Conclusions: Derived risks may be informative for counseling. Patterns of transmission may support evolving assumptions about genetic overlap for traditional categories.

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GENETICALLY ORIENTED studies of offspring of 2 psychiatric patients followed into adulthood represent a super-high-risk strategy compared with studies of children with only 1 affected parent. The dual-mating study permits calculating the effects of double predispositions on the lifetime morbid risk (age-corrected) in the offspring of couples with the same or different mental disorders. Such risks will be of use to genetic counselors to inform personal decisions with regard to marriage, family formation, adoption, and health insurance planning. Studies of the outcome in the offspring of parents with homotypic disorders, eg, schizophrenia × schizophrenia and bipolar affective disorder × bipolar affective disorder, may elucidate modes of transmission and possible genetic heterogeneity.[1,2] Matings between those with heterotypic disorders, eg, schizophrenia × bipolar disorder, may reveal the presence and risk of possible spectrum interforms or other atypical forms of parental criterion diagnoses in the offspring[3,4] and may be of interest to researchers intrigued by the overlap in offspring phenotypes between schizophrenia and bipolar affective disorder.[5-7]

Infrequent psychiatric dual-mating studies during the last century have relied on case histories of small clinical samples. They were all central European studies with diagnostic evaluations based on the German and Swiss concepts of Kraepelin and Bleuler, which are quite similar to the descriptions from the *International Classification of Diseases, Eighth Revision (ICD-8)* and *International Classification of Diseases, Ninth Revision (ICD-9)*.[8,9] Morbid risks (ie, age-corrected) of schizophrenia in offspring of 2 schizophrenic parents varied between 28% and 58% in 8 studies (on average, 48% in pooled data). Risk of manic-depressive disorder in offspring of 2 such

parents varied between 22% and 80% in 4 studies (on average 28% in pooled data),[4] that is, between 2 and 4 times the risk in contemporary studies of children with only 1 affected parent.[10] In offspring of 1 parent with schizophrenia and 1 parent with manic-depressive disorder, the risks of schizophrenia and manic-depressive disorder were similar to the risks in children with only 1 parent with schizophrenia or only 1 parent with manic-depressive disorder, 13% to 14% and 18% to 20% respectively.[3] The present study is conducted within the context of genetic epidemiology[11] to obtain maximum sample sizes, using all register-based diagnoses for each patient reported in the nationwide Danish Central Psychiatric Register.

METHODS

SOURCE OF DATA

A cohort of more than 2.6 million persons with a link to their biological parents, ignoring legal marital status, and with information on all psychiatric admissions among offspring and parents was established from 2 Danish registers with privacy guaranteed by meticulous safeguards in place. The Danish Civil Registration System[12] was established in 1968. All persons living in Denmark are assigned a unique identification number, and data on their date of birth, sex, vital status (continuously updated), and identity of parents and siblings are recorded. The identification number is used in all national registers, thus guaranteeing accurate linkage of information among registers.

The Danish Psychiatric Central Register contains data on psychiatric inpatient and outpatient admissions (currently about 650 000 persons with 2.8 million admissions), computerized since 1969 with complete registration from April 1, 1970, of all admissions to Danish psychiatric inpatient facilities; it has included outpatients since 1995.[13] As there are no private psychiatric inpatient or outpatient units, all admissions in Denmark are contained in the register. From 1966 until December 31, 1993, *ICD-8* was used for diagnostic classification[14]; *ICD-10* has been used since January 1, 1994.[15]

STUDY POPULATION

A population-based cohort of all persons born in Denmark, alive in 1968 or born later than 1968, and with a link to their mother and father was established from the Civil Registration System for a total of 3 391 018 persons. The investigation was restricted to persons who were aged 10 years before January 1, 2007, for a total of 2 685 301 persons and their parents. The number of unique parent couples (counted only once) was 1 278 977 couples, some of whom had more than 1 offspring.

STUDY DESIGN

Those who had ever received diagnoses of schizophrenia, bipolar affective disorder, or unipolar depressive disorder were identified from the Psychiatric Central Register among a group of parent couples with both parents ever having been admitted to a psychiatric facility from April 1, 1970, to January 1, 2007. For each of these groups of parent couples, their offspring, the eldest reaching age 52 years at follow-up, were checked in the register for admissions with similar or related diagnoses, and cumulative incidences were calculated.

For comparison, cumulative incidences were calculated in the offspring of couples with only 1 parent ever having been admitted to a psychiatric facility for the selected diagnoses and the other parent never having been admitted. To create base rates from the general population for comparison, cumulative incidences were calculated in the offspring of parent couples with neither parent ever having been admitted (cleaned population) and parent couples with no restrictions on parent diagnoses (uncleaned population).

Cumulative incidences of schizophrenia and bipolar disorder in offspring of both parents with heterotypic disorders were calculated in parent couples in which 1 parent was admitted for schizophrenia and the other parent was admitted for bipolar disorder to inform discussions about genetic overlap between schizophrenia and bipolar disorder. To get an estimate or impression of normality in the offspring of the various groups of parent couples, the cumulative incidences of any psychiatric diagnosis in the offspring were calculated.

Because both the parents and their offspring may have been admitted more than once with different diagnoses, they may appear in more than 1 of the groups of parent couples or offspring; thus the groups are not mutually exclusive. Furthermore, some of the offspring may have their own children in this longitudinal design; therefore, the same person may have dual status as both offspring and in one of the groups of parent couples.

ASSESSMENT OF PSYCHIATRIC DIAGNOSES

Parents and offspring were classified according to their diagnoses at discharge from admissions to inpatient or outpatient treatment facilities. Each admissions diagnosis was defined by the corresponding codes from *ICD-8* and *ICD-10* the first time the parents and offspring were recorded with that diagnosis in the Danish Psychiatric Central Register. Disorders were categorized as schizophrenia if they were given an *ICD-8* code of 295 (schizophrenia) or an *ICD-10* code of F20 (schizophrenia); as schizophrenia-related disorders if they received an *ICD-8* diagnosis of 297 (paranoid states), 298.3 (acute paranoid reaction), 298.9 (reactive psychosis unspecified), 299 (unspecified psychosis), 301.0 (paranoid personality disorder), 301.2 (schizoid personality disorder), or 301.83 and 301.84 (special Danish categories for borderline cases [*casus limitares pseudoneuroticae sive pseudopsychopathicae* or *casus limitares psychicae aliae*]), or an *ICD-10* code of F21 (schizotypal disorder), F22 (persistent delusional disorders), F23 (acute and transient psychotic disorders), F25 (schizoaffective disorders), F28 (other nonorganic psychotic disorders), F29 (unspecified nonorganic psychotic disorder), F60.0 (paranoid personality disorder), or F60.1 (schizoid personality disorder); as bipolar affective disorder if they received an *ICD-8* code of 296.1 (manic-depressive psychosis, manic type), 296.3 (manic-depressive psychosis, circular type), or 296.8 (manic-depressive psychosis, other), or an *ICD-10* code of F30 (manic episode), F31 (bipolar affective disorder), or F38.00 (mixed affective episode); as unipolar depressive disorder if they received an *ICD-8* code of 296.0 (involutional melancholia) or 296.2 (manic-depressive psychosis, depressed type), or an *ICD-10* diagnosis of F32 (depressive episode) or F33 (recurrent depressive disorder), and as any psychiatric disorder if they had received any *ICD-8* code between 290 and 315 or any *ICD-10* F code (F00-99).

STATISTICAL ANALYSIS

The incidence of psychiatric admission was calculated from the number of new cases occurring for each age in the cohort members.[16,17] Cumulative incidences at age t are calculated as

$$S(t) = \exp\left[-\sum_{t_i \le t} \lambda(t_i)\right]$$

$\lambda(t_i)$ is the incidence at time t_i, which is based on the Nelson-Aalen estimator.[18,19] The cumulative incidence reported in the tables and henceforth in the text can be interpreted as, at a given age,

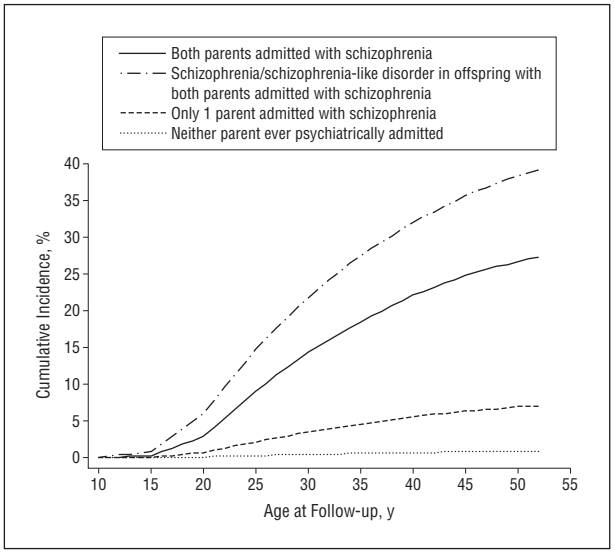

Figure 1. Cumulative incidence of admission with schizophrenia in offspring by age.

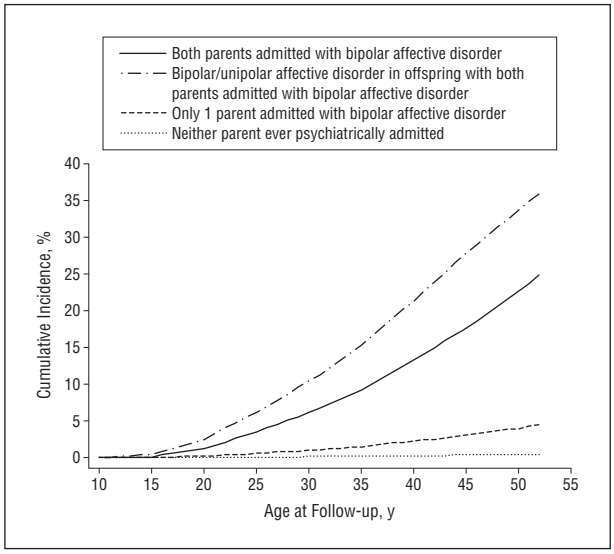

Figure 2. Cumulative incidence of admission with bipolar affective disorder in offspring by age.

the proportion of people in a population (eg, those with both parents admitted with schizophrenia) who have received a diagnosis prior to follow-up. Version 9 of SAS (SAS Institute Inc, Cary, North Carolina) was used in the estimation. Cumulative incidences cannot be calculated from the raw data on sample sizes.

ETHICS

This study was approved by the Danish Data Protection Agency. Because data available for register-based research do not include information that can lead to the identification of individuals, approval from the National Scientific Ethical Committee was not required.

RESULTS

RISK AS CUMULATIVE INCIDENCES OF DEVELOPING SCHIZOPHRENIA

For 196 couples with both individuals admitted with a diagnosis of schizophrenia (270 children), the cumulative incidence by age 52 years for 26 of their children being admitted with a diagnosis of schizophrenia was 27.3% (95% confidence interval [CI], 18.3-36.2) (**Figure 1**). Including schizophrenia-related disorders, the number of affected children increased to 40 and the cumulative incidence to 39.2% (95% CI, 28.8-48.6).

For 8006 couples with 1 of them admitted with schizophrenia and the other never having been admitted (13 878 offspring), the cumulative incidence for 473 of their offspring being admitted with schizophrenia was 7.0% (95% CI, 6.4-7.7). For 1 080 030 couples with neither individual ever having been admitted (2 239 551 offspring), 9384 offspring were admitted with schizophrenia; the cumulative incidence was 0.86% (95% CI, 0.83-0.88). In the general population with no restrictions on parental admissions (1 282 934 couples with 2 701 593 offspring and 14 938 offspring admitted with schizophrenia) the cumulative incidence was 1.12% (95% CI, 1.09-1.14). The last 2 values taken as base population rates correspond closely with the classic literature in genetic epidemiology.[11]

The risk estimated as cumulative incidence percentage by age 52 years of being admitted with a diagnosis of schizophrenia in offspring of 2 parents admitted with a diagnosis of schizophrenia is clearly (3.9 times) higher than in offspring with only 1 schizophrenic parent and 31.7-fold higher than in the general population with no parents ever having been admitted. Including schizophrenic spectrum disorders in the offspring raises the ratio to 45.6. The incidence in offspring with only 1 schizophrenic parent is also higher (8.2 times) than in the general population with no parents admitted.

In couples in which 1 individual was admitted with schizophrenia and the other was admitted with bipolar disorder, the cumulative incidence in their offspring admitted with schizophrenia was 15.6% (95% CI, 7.1-24.0). This is more than twice the value for the offspring of couples with 1 individual with schizophrenia. The difference shows a marked trend but is not statistically significant (overlapping CIs) because of low numbers. In couples with both parents admitted with bipolar disorder, the cumulative incidence in offspring for schizophrenia was 4.8% (95% CI, 0.2-9.4), 4 times the value for the general population.

RISK AS CUMULATIVE INCIDENCES OF DEVELOPING BIPOLAR AFFECTIVE DISORDER

For 83 couples with both individuals admitted with a diagnosis of bipolar disorder (146 offspring), the cumulative incidence of being admitted with bipolar disorder by age 52 years in 15 of their children was 24.95% (95% CI, 14.0-35.8) (**Figure 2**). With the inclusion of unipolar depressive disorder, the number of affected children increased to 24 and the cumulative incidence increased to 36.0%; 95% CI, 24.6-47.4).

In 11 995 couples with 1 individual admitted with bipolar disorder and the other never admitted, 400 in their 23 152 offspring were admitted with bipolar disorder; the

cumulative incidence was 4.4% (95% CI, 4.0-4.9). In 1 080 030 couples with neither individual ever admitted, 3452 of their 2 239 553 offspring were admitted with bipolar disorder; the cumulative incidence was 0.48% (95% CI, 0.46-0.51). In the general population with no restrictions on parental admissions (1 282 934 couples with 2 701 595 children of whom 5534 were admitted with bipolar disorder), it was 0.63% (95% CI, 0.60-0.66).

The risk of being admitted with a diagnosis of bipolar disorder, estimated as cumulative incidence percentage by age 52 years, is higher in offspring of 2 parents admitted with bipolar disorder than in offspring with only 1 bipolar parent (a ratio of 5.7) and 51.9-fold higher than in the general population with no parents ever admitted. Including unipolar depressive disorder in the offspring raises the ratio to 75.0. The incidence percentage in offspring with only 1 bipolar parent is also higher than in the general population with no parents ever admitted, a ratio of 9.2. In parent couples with 1 individual admitted with bipolar disorder and the other admitted with schizophrenia, incidence in their offspring was 11.7% (95% CI, 2.1-21.4) for bipolar disorder, which is 2 to 3 times higher than offspring of only 1 parent with bipolar disorder, though it was not significantly different because of a small number of couples with only 1 parent admitted with bipolar disorder. In couples with both individuals admitted with schizophrenia, incidence in their offspring was 10.8% (95% CI, 2.6-19.0) for bipolar disorder, about 10 times higher than in the general population.

SUMMARY CUMULATIVE INCIDENCE FOR ANY PSYCHIATRIC DIAGNOSIS

Cumulative incidence of any psychiatric diagnosis by age 52 years in offspring with both parents admitted with schizophrenia was 67.5% (95% CI, 59.0-75.9). One-third of these offspring had not been admitted for any mental disorder by age 52 years (ie, 100−67.5). For comparison, the concordance rate for schizophrenia in adult monozygotic twins is close to 50%.[10]

For individuals in which both of their parents were admitted with bipolar disorder, the cumulative incidence for any diagnosis was 44.2% (95% CI, 33.9-54.6); thus, more than half of the offspring at age 52 years had never been admitted. For offspring with neither parent ever having been admitted (>2.2 million offspring), the cumulative incidence for any psychiatric diagnosis was 11.9% (95% CI, 11.8-12.0), which means that in the general population, with no parents ever admitted, 88% of the offspring had had no psychiatric admissions by the age of 52 years.

For the general population with no restrictions on parents' psychiatric admissions, the uncleaned control group of parents, the cumulative incidence was 14.1% (95% CI, 14.0-14.2). Therefore, in the study population of offspring, only 1 in 7 had been admitted by age 52 years.

VARIABLE AGE AT ONSET AND DEVELOPMENT

By using cumulative incidences up to age 52 years as probabilities of receiving 1 of the selected psychiatric diagnoses, we have avoided the complications introduced to risk prediction by the fact that these major mental disorders have a variable age at onset that extends over decades, with mood disorders having an even wider range than the schizophrenia disorders. We provide examples of essential information by including diagnoses up to follow-up when our oldest offspring were aged 52 years in Figure 1 and Figure 2. The curves for schizophrenia appear to flatten out by age 45 years and we may be capturing a sufficient signal for the lifetime morbid risk by age 52 years. Figure 2 for bipolar disorder in the offspring of dual, single, and control couples is similar, but different in that it continues to rise at age 52 years. Thus, we are not finished with the risk period of developing illness in the offspring without 1 further observation, and we can only present the approximation to final risk from our empirical data.

COMMENT

Our contemporary cohort study is composed of more than 2.6 million persons and their biological parents in the Danish Civil Registration System. All parents and children were cross-matched against the Danish Psychiatric Central Register for ever having received a psychiatric diagnosis; each diagnosis included the first time individuals were recorded in the register with that diagnosis. For parent couples with both ever having received a diagnosis of schizophrenia or bipolar disorder, the incidences of similar disorders in their offspring were accumulated up to age 52 years. These incidences were compared with the cumulative incidences in offspring of couples with only 1 parent affected, and with base rates in the general population. To our knowledge, ours is the largest study ever conducted using high-risk and super-high-risk designs to quantify the effect on empirical risks as probabilities of receiving 1 of the selected diagnoses of these or any mental disorders, as a consequence of having 1 or 2 ill parents, compared with the general population and using the same diagnostic criteria across the sample. A few older studies with small clinical samples (before the use of criteria-based diagnoses) gave hints to what we might find.[4,20] The previous age-corrected rates for morbid risk are not directly comparable with our cumulative incidence probabilities, but may be converted to probabilities (*P*) by using $P = 1 - (e^{\wedge} - R)$, in which *R* indicates rates.[18] For schizophrenia, the converted probabilities are the same size as in our study. The pooled rates from the literature that used designs and methods comparable with ours[4] were 0.38 for certain schizophrenia and 0.48 for certain and probable schizophrenia in offspring of schizophrenic couples; they convert to probabilities of 0.32 and 0.38, respectively. The latter 2 values are similar to our cumulated incidence probability of 0.27 (95% CI, 0.18-0.36) for schizophrenia and 0.39 (95% CI, 0.29-0.49) for schizophrenia or schizophrenia-related disorders in the offspring of schizophrenic couples. The rates of morbid risk of manic-depressive psychoses from the comparable literature were 0.28 for certain and 0.39 for certain and probable manic-depressive psychosis in offspring of manic-depressive couples and convert to probabilities of 0.24 and 0.32, respectively, which are on a similar level with the cumulative incidence probability of 0.25 (95% CI, 0.14-0.36) for bipolar disorder and 0.36

(95% CI, 0.25-0.47) for bipolar disorder or unipolar depressive disorder in the offspring of bipolar couples.

Lichtenstein et al[21] recently reported risks for schizophrenia in a Swedish national cohort with a different approach and calculations of matched risks; they were not directly comparable with our results. The authors also provided risks calculated as ordinary morbidity risks similar to the literature, but omitted calculations on risk in offspring of dual matings.

Parent couples with heterotypic combinations—with 1 parent admitted with schizophrenia and the other with bipolar disorder—have cumulative incidences of schizophrenia and bipolar disorder in their offspring that show a higher trend than in offspring from couples with only 1 parent admitted with either schizophrenia or bipolar disorder. Although not statistically significant because of small numbers, these trends support recent findings that indicate a genetic overlap between schizophrenia and bipolar disorder.[5,22] Small samples did not allow analysis of cumulative incidence for schizoaffective disorders.

The register-based study is representative only of persons referred to inpatient or outpatient treatment in a nation that provides universal health insurance coverage for its citizens. For schizophrenia, practically all patients will be detected through the psychiatric services; of the schizophrenia-related disorders, the majority of patients will be detected, except for schizotypal disorder and for schizoid and paranoid personality disorder. For bipolar disorder, many moderate and most of the severe cases will be referred to treatment. For unipolar depressions, some moderate and recurrent and the majority of severe and psychotic cases, which comprise the majority of cases that eventually will turn out as bipolar,[23] will be referred and registered. The inclusion of outpatient diagnoses from 1995 onwards will not significantly change the number of diagnoses of schizophrenia, bipolar disorder, or severe and psychotic unipolar depressive disorder in those who will be admitted as inpatients. During the last quarter of a century, the number of inpatient beds in Denmark has been reduced from about 16 000 in 1984 to about 3400 in 2006, but the number of inpatient admissions has not changed owing to shorter admissions with early discharge and referral to follow-up treatment in an increasing number of community service outpatient clinics, in which they constitute most of the patients. The study diagnoses are only ascertained once, when received for the first time. A number of moderate nonpsychotic cases of unipolar depressive disorder may have been added with outpatient diagnoses, but the capacity of the community services has not allowed admissions of patients with mild or moderate cases. They will be taken care of in the primary health care system and therefore will not appear in the psychiatric register. All the same, unipolar depressive disorder was not included in this report in a separate analysis.

Comparing information on inpatients from up to 1995 with information including outpatients from up to 2006 shows very small differences in the cumulative incidences for schizophrenia and bipolar disorder, indicating that inclusion of outpatients does not influence these results to a significant degree. The inclusion of persons from age 10 years instead of 15 years was motivated by a wish to look at childhood disorders. The inclusion did not add much information and had very little influence on the resulting cumulative incidences.

The number of dual-mating couples was higher than expected from base rates, most likely because of assortative mating. There are fewer couples with only 1 parent admitted than might be expected, as usually seen in the literature, because marital couples represent a population screened for mental health.[24]

The validity of the register diagnoses has been investigated in a number of studies on representative samples from the register or from hospital clinics. For schizophrenia, the *ICD-8* diagnosis is restricted to severe, long-term cases. Compared with *ICD-10* criteria–based diagnoses, a considerable number of *ICD-10* cases of schizophrenia were previously diagnosed among *ICD-8* schizophrenia-related disorders.[25,26] The *ICD-10* schizophrenia diagnoses show high concurrent validity, virtually complete if schizophrenia-related disorders are included.[27] The validity is high for *ICD-8* manic-depressive disorder, *ICD-10* bipolar disorder, and melancholiform or psychotic depressions, but less so for mild to moderate depressions.[28] This means that the register diagnoses can be regarded as quite reliable for schizophrenia and bipolar disorder and also will permit the inclusion of schizophrenia-related disorders in a schizophrenia spectrum and unipolar disorder in a bipolar spectrum when diagnosed in couples' offspring.

We are mindful of the fact that familiality of a disease does not equate to obsolete ideas about genetic determinism. Evidence must converge from twin, family, and adoption studies to convince the scientist that the largest part of the familiality we observed in this study for schizophrenia and bipolar disorder was indeed attributable to genetic factors, and such data exist in abundance.[10]

The empirical risks of major mental disorders observed from this super-high-risk design, with both parents having been admitted for schizophrenia or bipolar disorder, are of such a magnitude that they command clinical and national public health attention in countries with health care roughly similar to Denmark's. The sample sizes available for our design project are unprecedented, yielding robust risks.

Such data as reported here must be handled with the utmost attention to privacy of health information, as they have been in Denmark. In countries without complete coverage by national health insurance, risk information could be misused in assigning premiums. Other uses of the information will involve personal decision making with regard to marriage, child bearing, adoption, and one's own prospects for the future. For all of these uses, well-informed counselors (genetic and otherwise) and health care workers concerned for the good of the individual person must be available. Lastly, no caretaker can be allowed to be ignorant of the Nazis' barbaric uses during the Third Reich of so-called genetic information to justify their eugenic policies of sterilization and murder.[29,30]

It is important to keep in mind that the yields from genetic epidemiology and the strategies implemented are applicable to groups of people, not to the individuals themselves. However, by joining advances in molecular genetics that are adapted for use in epidemiological genetic screening, our kinds of data with the risk groups described might lead to a large and rapid step forward in the understand-

ing of the etiologies of major mental disorders. The offspring of dual matings constitute a super-high-risk sample of psychosis; once affected, their DNA could be recovered from biobanks and used in current genomewide association studies using large-capacity single-nucleotide polymorphism chips. The DNA from stored Guthrie cards used to diagnose phenylketonuria has been amplified from available picograms to micrograms needed to conduct extensive single-nucleotide polymorphism genotyping.[31] The blood spots from Guthrie cards began to accumulate worldwide from 1962.[32,33] Ten states in the United States store these cards for more than 21 years. Perhaps custodians of other biobanks that have stored the Guthrie filter papers, mindful of privacy concerns, will be motivated to design projects combining epidemiological and molecular genetics so as to hasten progress in understanding and preventing complex diseases.

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