ORIGINAL ARTICLE

Full Spectrum of Psychiatric Outcomes Among Offspring With Parental History of Mental Disorder

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Context: While concordant parent/offspring risks for specific mental disorders are well established, knowledge of the broader range of psychiatric outcomes among offspring with parental history of mental disorder is lacking.

Objective: To examine the full range of mental health outcomes among offspring of parents with serious and other mental disorders compared with those whose parents had no such history.

Design: Population-based cohort study. Offspring were followed up from their 14th birthday for the development of mental disorders based on both outpatient and inpatient hospital data.

Setting: Danish population.

Participants: All offspring born in Denmark between 1980 and 1994 (N=865 078) with follow-up to December 2008.

Main Outcome Measures: Incidence rates, incidence rate ratios, and cumulative incidences for offspring psychiatric outcomes.

Results: Parental serious mental disorder (SMD) (nonaffective or affective psychosis) was found to be positively associated with virtually all offspring psychiatric outcomes, including those not hitherto regarded as clinically related. Offspring of parents without SMD but with a history of "other mental disorder" were also found to be at increased risk of developing a range of mental disorders. The strongest associations were found where both parents had a history of mental disorder (eg, offspring of 2 parents with SMD were 13 times more likely to develop schizophrenia). Elevated risks were not confined to concordant parent/offspring disorders (eg, offspring of 2 parents with SMD were 8 times more likely to develop substance misuse disorders).

Conclusions: The impact of parental history of mental disorder was not confined to elevated offspring risk of concordant disorders but rather offspring are at increased risk of a wide range of mental disorders, particularly those with 2 affected parents. Our results imply an important role for etiological factors giving rise to broad, as well as specific, familial vulnerabilities. These findings also have potential implications for diagnostic classification.

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PARENTAL MENTAL DISORDER can have a dramatic impact on the next generation.[1,2] In particular, offspring of parents with major mental disorders are at elevated risk of developing a mental disorder. Family, twin, adoption, and high-risk cohort studies have confirmed the high risk of concordant disorders among offspring with familial history of serious mental disorders such as schizophrenia and bipolar disorder, with much of this risk having been attributed to genetic rather than environmental factors.[3-12]

While previous research has focused on the risks of concordant parent/offspring disorders, there is emerging evidence to indicate that genes predisposing to clinically related disorders may be shared.[11,13,14] Recent results from a Swedish family study add further weight to the notion that schizophrenia and bipolar disorder share genes in common, to the extent that the authors call for a reevaluation of the current diagnostic distinction between the 2 disorders.[15] Evidence of an even broader range of psychiatric outcome risk among offspring with a family history of mental disorder is also emerging. Several of the high-risk (for serious mental disorder) cohorts have now been followed up through adulthood to determine rates of mental disorder. In both the Copenhagen and New York high-risk cohorts, offspring of mothers with schizophrenia were found not only to have elevated risks for schizophrenia but also for a range of psychotic, affective, and personality disorders.[16,17] Offspring born to mothers with schizophrenia in the Helsinki High-Risk Study were followed up to age 35 to 39 years, with 23.1% found to have themselves developed mental disorder (6.7% had

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developed schizophrenia, 10.6% had developed a nonpsychotic disorder).[18] Thus, there appears to be some evidence that, at least among those at high risk for serious mental disorders, individuals may also be at increased risk of disorders that have hitherto been regarded as clinically unrelated.

The aim of the current study, based on data from the Danish population registers, was to examine the full range of mental health outcomes in a large representative national cohort among offspring of parents with a history of mental disorders compared with offspring of parents without a history of psychiatric treatment contacts.

METHODS

STUDY POPULATION

We used data from the Danish Civil Registration System[19] to obtain a large and representative set of data on residents of Denmark 14 years or older. The Civil Registration System contains data for each individual on name, sex, date of birth, place of residence, citizenship, continuously updated information on vital status, and the Centrale Person Register numbers of parents and spouses, along with many other variables. The Centrale Person Register number is used as a personal identifier in all national registers, enabling accurate linkage between registers. Our study population included all persons born in Denmark during the period between January 1, 1980, and December 31, 1994, who were alive on their 14th birthday and whose maternal identity was known (N=865 078 persons). Thus, 568 (0.07%) were excluded from the sample on the basis of unknown maternal identity.

ASSESSMENT OF MENTAL DISORDER IN OFFSPRING AND THEIR PARENTS

Individuals within the study cohort and their parents were linked via their Centrale Person Register numbers to the Psychiatric Central Register, which contains data relating to all admissions to psychiatric hospitals since 1969 and all outpatient contact data since 1995.[20] From April 1969 to December 1993, the diagnostic system used by clinicians in routine practice was the *International Classification of Diseases, Eighth Revision* (*ICD-8*),[21] and from January 1994, the diagnostic system used was the *International Statistical Classification of Diseases, 10th Revision* (*ICD-10*).[22] Cohort members were classified with a mental disorder if they had been admitted to a psychiatric hospital or had received outpatient care. The full spectrum of possible mental disorders was considered, including the following: schizophrenia (*ICD-10* code F20), schizophrenia spectrum disorders (*ICD-10* codes F21-23 and F29), schizoaffective disorder (*ICD-10* code F25), bipolar disorder (*ICD-10* codes F30-31), substance use disorders (*ICD-10* codes F10-19), affective disorders (*ICD-10* codes F32-34 and F38-39), anxiety and somatoform disorders (*ICD-10* codes F40-45 and F48), and personality disorders (*ICD-10* codes F60-61). Two additional outcome categories were also examined: other psychiatric contact (defined as contact with inpatient or outpatient psychiatric services with a diagnosis other than those previously considered) and any psychiatric contact (a category representing offspring contact with psychiatric services for any reason, including both the specific disorders examined and the "other" category). Multiple disorders were recorded if developed by offspring. For each offspring mental disorder outcome, the date of onset was defined as the first day of the first contact (inpatient or outpatient) with the diagnosis of interest.

CLASSIFICATION OF OFFSPRING TO PARENTAL HISTORY OF MENTAL DISORDER EXPOSURE GROUPS

Parents were classified as having a history of mental disorder if they had been admitted to a psychiatric hospital or had been in outpatient treatment (after 1995) for 1 of the following conditions: nonaffective psychosis (*ICD-8* codes 295.0-295.78, 295.80-295.99, 297.0-297.99, 298.39, and 301.83 and *ICD-10* codes F20-23 and F29), affective psychosis (*ICD-8* codes 296.19 and 296.39 and *ICD-10* codes F30-31), or any other psychiatric contact. Only diagnoses given prior to the child's 14th birthday were considered. If a parent had been diagnosed with both an affective and nonaffective psychosis, the diagnosis most recent to the child's 14th birthday was used. Exposure groups were defined on the basis of the type of parental mental disorder and the number of parents affected to create the following 7 exposure categories:

1. Two parents with serious mental disorder (nonaffective psychosis or affective psychosis).
2. One parent with serious mental disorder, second parent with any other psychiatric contact.
3. One parent with nonaffective psychosis, other without a history of psychiatric contact.
4. One parent with affective psychosis, other without a history of psychiatric contact.
5. Two parents with any other psychiatric contact.
6. One parent with any other psychiatric contact, other without a history of psychiatric contact.
7. No history of mental disorder in either parent.

Incidence rates for each exposure group were compared with the reference group, consisting of those offspring without parental history of any psychiatric contact.

STATISTICAL ANALYSIS

Individuals within the offspring cohort were followed up from their 14th birthday until onset of the outcome in question, death, emigration from Denmark, or December 31, 2008, whichever came first. The incidence rate ratios (IRRs) for each offspring mental disorder outcome were estimated by log linear Poisson regression.[23,24] All IRRs were adjusted for calendar period, age, and sex, and since age-related incidence rates were found to vary by sex, we also adjusted for the interaction between age and sex. Age and calendar period were treated as time-dependent variables,[25] whereas all other variables were treated as variables independent of time. Age was categorized as 14, 15, 16, 17, 18, 19, 20 to 21, 22 to 23, 24 to 25, and 26 to 28 completed years and calendar year of diagnosis was categorized in one 4-year band from 1994 and thereafter in 2-year bands, except where stated otherwise (**Table 1**). *P* values and 95% confidence intervals (CIs) were based on likelihood ratio tests.[25] The adjusted score test[26] was used to assess whether the regression models were subject to overdispersion. Adjustment was made for the apparent effect of "unknown father" status since this was found to be independently associated with an increased rate of offspring psychiatric outcomes. Interaction by parental sex was also examined for each parental-offspring disorder association. To test the appropriateness of the offspring age at follow-up (14 years), a sensitivity analysis was undertaken for each comparison such that analyses were repeated using a cohort born in the period 1984 to 1997 and followed up from age 10 years. No benefit of using the secondary cohort was found for any of the analyses, indicating that an earlier age at follow-up commencement was not warranted. Cumulative incidence for the offspring outcome of "any psychiatric contact" was calculated using Poisson regression based on a model of competing risk[27] using age as the time scale and with separate

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Table 1. IRRs for Offspring Psychiatric Disorders According to Parental Mental Disorder[a]

Offspring Outcome	Parental Mental Disorder Exposure						
	Both Parents SMD	1 Parent SMD; 1 Other Mental Disorder	1 Parent Nonaffective Psychosis	1 Parent Affective Psychosis	Both Parents Other Mental Disorder	1 Parent Other Mental Disorder	No History of Mental Disorder in Either Parent
Schizophrenia							
No. of cases	10	26	108	12	57	486	2249
IRR (95% CI)	13.15 (6.58-23.11)	5.86 (3.88-8.43)	4.07 (3.34-4.91)	1.48 (0.79-2.49)	3.76 (2.86-4.84)	2.37 (2.37-2.61)	1 [Reference]
P value	<.001	<.001	<.001	.17	<.001	<.001	
Schizophrenia spectrum							
No. of cases	11	39	129	33	85	589	2898
IRR (95% CI)	11.06 (5.74-18.97)	6.67 (4.78-9.01)	3.74 (3.12-4.45)	3.09 (2.15-4.28)	4.21 (3.37-5.19)	2.18 (2.00-2.38)	1 [Reference]
P value	<.001	<.001	<.001	<.001	<.001	<.001	
Bipolar disorder							
No. of cases		6	29	29	6	135	582
IRR (95% CI)	[b]	5.31 (2.10-10.81)	4.18 (2.82-5.95)	14.23 (9.58-20.26)	1.55 (0.61-3.16)	2.55 (2.10-3.06)	1 [Reference]
P value		<.001	<.001	<.001	.29	<.001	
Schizoaffective disorder							
No. of cases			10		5	48	207
IRR (95% CI)	[b]	[b]	4.12 (1.03-7.35)	[b]	3.69 (1.31-8.04)	2.58 (1.87-3.51)	1 [Reference]
P value			<.001		.004		
Affective disorders							
No. of cases	11	62	193	92	206	1855	10 689
IRR (95% CI)	2.77 (1.44-4.74)	2.91 (2.25-3.70)	1.52 (1.31-1.75)	2.38 (1.93-2.90)	2.79 (2.42-3.20)	1.87 (1.78-1.96)	1 [Reference]
P value	.001	<.001	<.001	<.001	<.001	<.001	
Anxiety disorders							
No. of cases	22	149	513	169	508	4067	20 124
IRR (95% CI)	3.10 (1.98-4.58)	3.81 (3.22-4.45)	2.19 (2.00-2.38)[c]	2.32 (1.99-2.69)	3.73 (3.41-4.07)	2.19 (2.12-2.26)	1 [Reference]
P value	<.001	<.001	<.001	<.001	<.001	<.001	
Personality disorders[d]							
No. of cases	13	81	259	50	229	1876	8484
IRR (95% CI)	4.44 (2.44-7.31)	5.07 (4.04-6.27)	2.60 (2.29-2.93)	1.67 (1.25-2.18)	4.18 (3.65-4.75)	2.45 (2.33-2.58)	1 [Reference]
P value	<.001	<.001	<.001	<.001	<.001	<.001	
Substance misuse							
No. of cases	14	79	184	51	190	1324	5200
IRR (95% CI)	8.16 (4.59-13.22)	7.76 (6.16-9.62)	3.02 (2.59-3.48)	2.71 (2.03-3.53)	5.44 (4.69-6.27)	2.80 (2.63-2.97)	1 [Reference]
P value	<.001	<.001	<.001	<.001	<.001	<.001	
Other psychiatric contact[d]							
No. of cases	18	112	417	100	330	2908	15 342
IRR (95% CI)	4.16 (2.52-6.39)	3.90 (3.22-4.67)	2.43 (2.21-2.68)[c]	1.79 (1.46-2.17)	3.18 (2.84-3.54)	2.05 (1.97-2.13)	1 [Reference]
P value	<.001	<.001	<.001	<.001	<.001	<.001	
Any psychiatric contact[d]							
No. of cases	37	249	945	278	816	7409	39 948
IRR (95% CI)	3.61 (2.57-4.90)	3.69 (3.25-4.16)	2.20 (2.06-2.34)[c]	2.03 (1.80-2.28)	3.33 (3.11-3.57)	2.10 (2.05-2.15)	1 [Reference]
P value	<.001	<.001	<.001	<.001	<.001	<.001	

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; SMD, serious mental disorder (includes nonaffective and affective psychoses).
[a] All IRRs were adjusted for "unknown father" status, calendar period, age, sex, and the interaction between age and sex.
[b] Insufficient number of cases to calculate IRR estimate (n<5).
[c] Significant difference by sex of parent.
[d] Narrower age bands used for adjustment.

baselines for each sex (to produce a plot of cumulative incidence by age). Cumulative incidence at the 28th birthday was also calculated for each of the offspring outcomes, separately for males and females. Only those offspring with a known father were included in these analyses.

RESULTS

DESCRIPTIVE RESULTS

A total of 865 078 offspring born in Denmark between 1980 and 1994 (who were also alive and residing in Denmark at the age of 14 years) were included in the study. The cohort was followed up for a total of 5 774 938 person-years; the longest period of any individual follow-up was 29 years (from birth in 1980 until the end of follow-up in December 2008; follow-up ranged from 15-29 years). Around 5% of offspring (n=49 682) had at least 1 contact with either inpatient or outpatient psychiatric services in Denmark after their 14th birthday and before the end of the follow-up period in 2008. The most common offspring psychiatric diagnosis category was anxiety and somatoform disorders (n=25 552; 2.95%), followed by "other psychiatric contact" (n=19 227; 2.22%), affective disorders (n=13 108; 1.52%), personality disorders (n=10 992; 1.27%), substance misuse (n=7042; 0.81%), schizophrenia spectrum (n=3784; 0.44%), schizophrenia (n=2948; 0.34%), bipolar disorder (n=788; 0.09%), and schizoaffective disorder

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(n=276; 0.03%). Of those offspring who made contact with services for any reason, almost one-fifth (19.6%) had a parental history of mental disorder. A little more than 1% of offspring with mental disorders did not have a registered father and this was consistently found to be a risk factor in itself for offspring disorder (as a result this factor was included as a covariate in all analyses).

INCIDENCE RATES ACCORDING TO PARENTAL MENTAL DISORDER HISTORY

Incidence rate ratios for each of the 10 offspring outcomes according to parental mental disorder are presented in Table 1 (except where n<5). For almost all of the 10 outcomes within each of the 6 parental exposure groups, the incidence rate was increased compared with the unexposed group (those without parental history of mental disorder).

Increased rates of specific offspring mental disorders were not confined to those exposed to concordant parental mental disorder; increased rates were seen across the spectrum of diagnoses for each of the parental exposure categories. There was evidence of 2 dose-response effects. First, parental history of serious mental disorder (nonaffective and affective psychoses) conferred a higher risk than parental history of "other mental disorder," and second, 2 affected parents conferred a higher risk than 1 affected parent. The highest risks were seen for those offspring with 2 parents diagnosed with serious mental disorder. This was particularly true for concordant disorder outcomes, ie, risk of schizophrenia (IRR, 13.15; 95% CI, 6.58-23.11) and schizophrenia spectrum (IRR, 11.06; 95% CI, 5.74-18.97), but was also true for clinical outcomes not traditionally thought to be related, such as substance misuse disorders (IRR, 8.16, 95% CI, 4.59-13.22), for example.

With regard to serious mental disorders, the greatest evidence for concordant risk was seen for affective psychosis; those offspring exposed to 1 parent with affective psychosis had an incidence rate of bipolar disorder 14.23 times higher than those without parental mental disorder (95% CI, 9.58-20.26). In contrast to the pattern for affective psychosis, having a parent with nonaffective psychosis did not result in a pattern reflecting such strong concordance, the increased risk for schizophrenia being similar to that for bipolar disorder (IRR for schizophrenia, 4.07, 95% CI, 3.34-4.91; IRR for bipolar disorder, 4.18, 95% CI, 2.82-5.95).

Somewhat surprisingly, the general tendency for risk of offspring disorder to be increased with increased severity of parental disorder did not hold true for many of the non-SMD offspring outcomes nor for the outcome "any psychiatric contact." When only 1 parent had a disorder, the risk of "any psychiatric contact" was more than twice that of offspring without parental disorder history, regardless of the nature of the parental disorder. The same lack of effect for severity of parental disorder was also seen when both parents had a disorder.

INTERACTION BY PARENTAL SEX

There was little evidence of any interaction by parental sex, although the test for interaction could not be carried out for some comparisons because of the small numbers of cases. The impact of having an ill father vs an ill mother was found to be significant for the following exposure-outcome associations: 1 parent with nonaffective psychosis and 3 of the offspring outcomes, anxiety disorder, other mental disorder, and any psychiatric contact. In each case, risk was higher for offspring with a maternally affected parent.

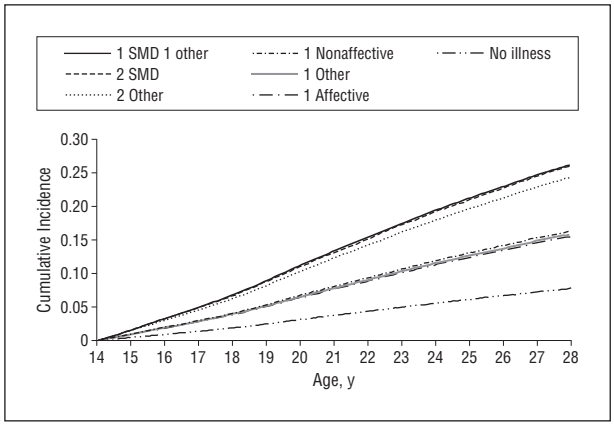

Figure 1. Cumulative incidence of any psychiatric contact for male offspring. Seven curves are presented on the same graph, 1 for each parental disorder exposure group as well as the reference group. Affective indicates affective psychosis; Nonaffective, nonaffective psychosis; and SMD, serious mental disorder.

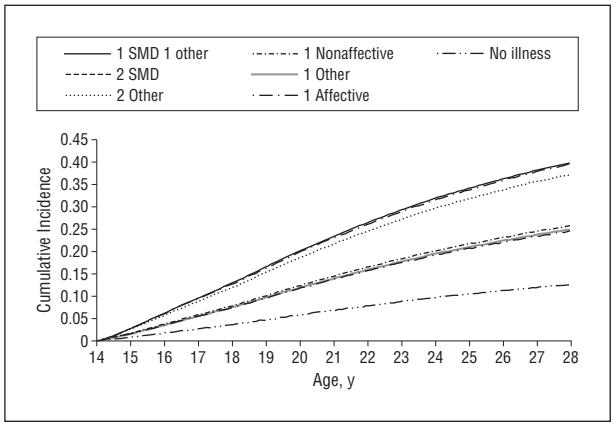

Figure 2. Cumulative incidence of any psychiatric contact for female offspring. Seven curves are presented on the same graph, 1 for each parental disorder exposure group as well as the reference group. Affective indicates affective psychosis; Nonaffective, nonaffective psychosis; and SMD, serious mental disorder.

CUMULATIVE INCIDENCE PATTERNS AMONG OFFSPRING

In addition to the results contained in Table 1 for offspring with any psychiatric contact (last row of Table 1), cumulative incidence for this outcome is graphically presented in **Figure 1** and **Figure 2** (see **Table 2** for cumulative incidences for each of the offspring outcomes). For each exposure category and at each age, the cumulative incidence measures the probability that an individual developed the disease in question, ie, the cumulative incidence measures an absolute risk rather than relative risk. A similar pattern by age was seen for each of the parental exposure groups. All exposure groups appeared to have an elevated risk of "any psychiatric contact" at all ages compared with the reference category. For both male and female offspring, the pattern of elevated risks across ex-

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Table 2. Cumulative Incidences by the 28th Birthday for All Offspring Psychiatric Outcomes According to Parental Mental Disorder by Sex

Offspring Outcome	Parental Mental Illness Exposures, % (95% CI)						
	Both Parents SMD	1 Parent SMD; 1 Other Mental Disorder	1 Parent Nonaffective Psychosis	1 Parent Affective Psychosis	Both Parents Other Mental Disorder	1 Parent Other Mental Disorder	No History of Mental Disorder in Either Parent
Schizophrenia							
Men	9.35 (3.82-14.89)	4.26 (2.64-5.89)	2.85 (2.29-3.41)	1.11 (0.48-1.74)	2.19 (1.61-2.76)	1.73 (1.55-1.90)	0.57 (0.68-0.77)
Women	7.46 (2.99-11.92)	3.37 (2.08-4.66)	2.26 (1.80-2.71)	0.88 (0.38-1.38)	2.76 (2.04-3.48)	1.36 (1.22-1.51)	0.72 (0.53-0.61)
Schizophrenia spectrum							
Men	9.45 (4.14-14.86)	5.82 (4.03-7.62)	3.20 (2.62-3.77)	2.70 (1.77-3.63)	3.74 (2.93-4.54)	1.93 (1.74-2.11)	0.87 (0.81-0.92)
Women	7.95 (3.42-12.45)	4.86 (3.35-6.37)	2.66 (2.17-3.15)	2.25 (1.47-3.03)	3.11 (2.44-3.79)	1.60 (1.44-1.76)	0.72 (0.67-0.77)
Bipolar disorder							
Men	[a]	0.81 (0.15-1.47)	0.62 (0.37-0.87)	2.18 (1.33-3.03)	0.24 (0.05-0.43)	0.39 (0.30-0.48)	0.15 (0.12-0.17)
Women	[a]	1.39 (0.27-2.50)	1.06 (0.65-1.47)	3.72 (2.32-5.12)	0.41 (0.08-0.74)	0.67 (0.53-0.81)	0.25 (0.22-0.29)
Schizoaffective disorder							
Men	[a]	[a]	0.19 (0.06-0.31)	[a]	0.16 (0.01-0.31)	0.12 (0.07-0.16)	0.05 (0.03-0.06)
Women	[a]	[a]	0.34 (0.12-0.55)	[a]	0.30 (0.03-0.56)	0.21 (0.14-0.28)	0.08 (0.06-0.10)
Affective disorders							
Men	5.21 (2.21-8.22)	5.44 (4.11-6.78)	2.78 (2.38-3.19)	4.50 (3.58-5.41)	5.28 (4.55-6.01)	3.45 (3.26-3.67)	1.82 (1.74-1.89)
Women	12.35 (5.52-19.18)	12.87 (9.88-15.87)	6.72 (5.78-7.65)	10.71 (8.63-12.79)	12.49 (10.88-14.11)	8.32 (7.92-8.73)	4.41 (4.29-4.54)
Anxiety disorders							
Men	10.92 (6.61-15.23)	13.26 (11.25-15.27)	7.65 (6.97-8.32)	8.27 (7.05-9.49)	13.13 (12.01-14.24)	7.77 (7.46-8.08)	3.53 (3.43-3.64)
Women	20.69 (13.01-28.38)	24.81 (21.35-28.27)	14.74 (13.54-15.95)	15.89 (13.67-18.11)	24.58 (22.70-26.46)	14.96 (14.48-15.44)	6.96 (6.82-7.10)
Personality disorders							
Men	6.38 (3.02-9.74)	7.24 (5.71-8.78)	3.80 (3.32-4.27)	2.48 (1.79-3.16)	6.01 (5.23-6.80)	3.56 (3.36-3.77)	1.46 (1.40-1.52)
Women	14.26 (7.09-21.43)	16.10 (12.88-19.32)	8.64 (7.61-9.67)	5.69 (4.15-7.22)	13.48 (11.84-15.12)	8.12 (7.74-8.50)	3.38 (3.29-3.47)
Substance misuse							
Men	16.13 (8.34-23.87)	15.26 (12.13-18.39)	6.09 (5.20-6.98)	5.71 (4.18-7.24)	10.10 (9.48-12.51)	5.72 (5.37-6.08)	2.04 (1.96-2.13)
Women	8.07 (4.00-12.14)	7.62 (5.97-9.27)	2.96 (2.51-3.41)	2.77 (2.01-3.54)	5.42 (4.63-6.21)	2.78 (2.58-2.98)	0.98 (0.93-1.04)
Other psychiatric contact							
Men	11.68 (6.61-16.76)	11.07 (9.12-13.02)	6.83 (6.17-7.49)	5.29 (4.28-6.31)	9.19 (8.22-10.15)	5.90 (5.65-6.15)	2.86 (2.78-2.94)
Women	17.25 (10.01-24.49)	16.37 (13.59-19.15)	10.22 (9.27-11.18)	7.96 (6.46-9.46)	13.66 (12.27-15.04)	8.85 (8.51-9.19)	4.32 (4.23-4.42)
Any psychiatric contact							
Men	25.69 (18.58-32.80)	26.26 (23.45-29.06)	16.26 (15.28-17.24)	15.48 (13.79-17.17)	24.25 (22.77-25.73)	15.77 (15.37-16.17)	7.69 (7.56-7.82)
Women	39.10 (29.38-48.82)	39.87 (36.07-43.68)	25.65 (24.22-27.09)	24.49 (21.98-27.00)	37.11 (35.09-39.14)	24.93 (24.39-25.47)	12.52 (12.36-12.68)

Abbreviations: CI, confidence interval; SMD, serious mental disorder (includes nonaffective and affective psychoses).
[a] Insufficient number of cases.

posure groups was very similar. The highest absolute risk at all ages for either offspring sex was seen among those with 1 parent affected by SMD and the other affected by "other mental disorder." As offspring age increased, risk among the 6 exposure groups increased relative to the unexposed group (ie, the exposure groups become increasingly divergent from the reference group) and 2 groups of exposure appeared to develop: those 3 groups with 2 parents affected by disorder had a higher risk compared with the 3 exposure groups defined by having 1 affected parent. The cumulative incidence at the 28th birthday appeared to be higher for female than male offspring for almost all outcomes (Table 2).

COMMENT

In this study of 865 078 offspring, we found evidence of parental mental disorder conferring increased risk not only of concordant disorders but also of nonclinically related disorders among offspring. We also found that the increased risk of offspring disorder was not confined to those with parents with serious mental disorders. This is the first study, to our knowledge, that considers the broad panorama of mental disorders in both parents and offspring.

STRENGTHS AND LIMITATIONS

The main strengths of this study lie in the nature of the data used and the broad range of mental disorders considered. The sample size was large and was obtained from population-based registers, allowing sufficient power to examine even rare parent-offspring diagnostic associations, without the problems of bias inherent in studies that involve selected samples. The Danish registers have an almost complete national coverage and follow-up, with linkage between registers resulting in virtually no loss of individuals.[19]

Reliance on routinely acquired clinical information has its limitations, particularly with regard to the validity and

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reliability of diagnoses. Reassuring results have been obtained from studies that have assessed the validity of diagnoses acquired from the Danish Psychiatric Central Register.[28-30] In addition, diagnostic data acquired from routinely collected clinical information do have real advantages in terms of generalizing research findings to clinical settings and in relation to the minimization of information bias, which is often an unavoidable limitation associated with other measurement methods. Since offspring were followed up for psychiatric contact events from 1994 at the earliest, the period of outcome data collection was covered by the *ICD-10* classification system only. In addition, a significant strength of the study is the fact that outpatient as well as inpatient contact data were available throughout almost the entire follow-up period. National register-based studies often rely on hospital inpatient data alone. Those receiving outpatient treatment only are necessarily excluded, an issue that is particularly problematic for disorders where the likelihood of inpatient contact is low (eg, anxiety disorders) and in countries that have undergone a process of deinstitutionalization, with an increasing emphasis on community-based intervention and reduction in inpatient bed numbers. It may, of course, be argued that the validity of diagnoses based on outpatient contact alone might differ from those based on inpatient clinical assessments. Although we were unable to assess the extent to which this might be true, any differences will reflect those that occur in the context of routine clinical practice. Also, in our study we were unable to identify parents with mental disorder who were in contact with mental health services on an outpatient basis exclusively prior to 1995 and who had no contact at all after 1995, or who only had contact with mental health services prior to 1969. As a consequence, our estimates of risk are conservative since a proportion of parents will have been misclassified as not having a mental disorder. The importance of such misclassification bias will be greater for disorders of greater frequency, while for serious mental disorder, we would expect little impact.[31,32] In addition, we had to convert parental diagnoses made during the *ICD-8* period into *ICD-10*-equivalent categories, a necessity that may have introduced nondifferential error in the classification of offspring to particular parental mental disorder exposure groups, although we used relatively broad categories for these groups so any error is likely to be limited.

There is potential for bias in our study because of the likelihood that offspring with a disorder born to parents with known mental disorder may be more likely to make contact with mental health services simply because of the contact already made by their parents. This bias would overestimate any parent-offspring associations. It may well have a greater impact on concordant disorder associations on the basis that parents or those caring for them may be more likely to recognize symptoms in offspring that are similar to those experienced by their parent(s). However, the diagnosis of serious mental disorders in offspring is less likely to be affected by this bias, because for these disorders, it is arguably reasonable to assume that the vast majority of cases in the population will come in contact with services, at least at the outpatient level, at some point in their disorder course. This is, of course, not true for common mental disorders, such as mild anxiety and depressive disorders, which are frequently managed in primary care or may not lead to health contacts at all. In addition, for all offspring diagnoses it is possible that clinicians might take family history into account when making diagnostic decisions, leading to an overestimation of concordance. A related limitation of the current study is the duration of follow-up. The oldest age for offspring at the end of follow-up was almost 29 years, and thus, we are unable to report lifetime risks for offspring. There is no evidence that our study was underpowered by the timing of follow-up given that almost all exposure groups were significantly associated with all outcomes examined but the precise pattern of results may well be altered by a longer follow-up period. Our findings regarding disorders often diagnosed later in life (eg, bipolar disorder) may only be applicable to early-onset cases. This may be of particular relevance to our finding of strong parent-offspring concordance for bipolar disorder.

Finally, it was not possible to confirm whether registered fathers were also the biological fathers for offspring in the cohort. The impact of any fathers wrongly assumed to have paternity for registered offspring would be to underestimate any paternal-offspring associations due specifically to genetic effects, although estimated rates of incorrect paternity have been reported as low and thus the impact on our study is likely to be minimal.[33]

MAIN FINDINGS

Overall, our results appear to demonstrate 2 general patterns of parent-offspring association. One is a relatively modest elevation of risk across exposure groups for all offspring outcomes. The second appears to be effectively superimposed on this general elevation in risk and reflects the impact of 2 dose-response relationships: (1) the impact of having 2 compared with 1 affected parent and (2) the impact of parental history of serious mental disorder compared with other mental disorders, particularly for offspring psychotic outcomes.

The fact that risk in offspring was not confined to concordant disorders calls into question the view that familial risk is mediated by disorder-specific causes, whether they are genetic or environmental. There has been much debate, for example, about whether nonaffective and affective psychoses have genes in common or can be differentiated by their distinct genetic bases. Increasingly, the findings of molecular genetic studies, particularly large-scale association studies, appear to support the former hypothesis.[13,34] Although inconsistent findings have been reported from genetic epidemiological studies previously, a recent population-based family study also found evidence of shared genetic risk for schizophrenia and bipolar disorder.[15] Data from the Danish population registers have also been used to demonstrate that risk for schizophrenia in particular is not limited to those with a parent who also has schizophrenia but is increased among those whose parents have a range of other mental disorders (population attributable risk for the latter 27.1% vs 6.0% for the former).[35] Evidence was also found to support the notion of substantial overlap between schizophrenia and bipolar disorder in a Danish study of comorbidity rates.[36] Consistent with the shared-genetic hypothesis, we found

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that those individuals with a parental history of nonaffective psychosis had an increased risk of bipolar disorder (IRR, 4.18) and that those with parental affective psychosis had an increased risk of both schizophrenia (IRR, 1.48; nonsignificant) and schizophrenia spectrum disorders (IRR, 3.09). Interestingly, we found strong evidence for concordant disorder risk for bipolar disorder but only moderate concordant risk for schizophrenia and schizophrenia spectrum disorders. Beyond the evidence of previous studies, we are able to add that shared risk was seen in our study across the full panorama of mental disorders. Individuals with parental history of non–serious mental disorder had a raised risk of schizophrenia and bipolar disorder, while those with parental serious mental disorder had a raised risk not only of schizophrenia or bipolar disorder but of nonclinically related disorders ranging from affective and anxiety disorders to substance misuse and personality disorder. This is consistent with the results of several high-risk cohort studies that have also found evidence of a broad range of psychiatric outcomes for offspring, at least of parents with schizophrenia.[16-18] It is also consistent with the recent finding that co-twins discordant for schizophrenia have elevated rates of nonpsychotic disorders, including depression and anxiety.[37]

We were surprised to find that while severity of parental mental disorder elevated offspring risk of psychotic disorders, it did not appear to have the same impact on offspring risk of nonpsychotic mental disorders. Certainly having 2 parents with a disorder conferred a greater risk than having only 1 parent with mental disorder for these nonpsychotic outcomes but the nature of parental disorder appeared less important. It might be argued that this differential effect of parental disorder severity reflects instead an effect of concordance but we did not find that parental "other mental disorder" elevated risk of nonpsychotic offspring disorders above that associated with parental serious mental disorder. Our parental mental disorder categories were, however, relatively broad, and thus, a more detailed examination of parent-offspring associations might be required to further clarify this issue.

Given the nature of our study, we were not able to separate the roles played by genetic and environmental mechanisms with regard to explaining familial risk. It is important to recognize of course that not all familial risk is mediated through genetic factors. Environmental factors and the interaction between genes and the environment are likely to be important mediators also. We hypothesized that maternal history of disorder would confer a greater risk of offspring disorder compared with paternal disorder based on the premise that the role of environmental factors might arguably be greater for offspring born to affected mothers, although genes might also be implicated in any such parent of origin effect if found. In any event, we did not find any substantial evidence for interaction by parental sex. The offspring disorders examined in our study vary in the degree to which they are thought to be genetically influenced, and thus, the role of environmental factors might well be greater for some than others.[38-40] Putative environmental factors that might mediate the parent-offspring mental disorder associations would include obstetric complications,[41] early parental loss[10] or other life events, parental separation,[42] parenting difficulties potentially including childhood maltreatment or trauma,[43] urbanicity,[44] and other social or socioeconomic factors.[45] While beyond the scope of our study aims, future research could examine the role of such factors to further understanding of familial risk for mental disorder.

Although the focus of our study was on understanding familial risk for mental disorder, we confirmed that the vast majority of individuals who develop mental disorder have no parental history of mental disorder. Around four-fifths of those offspring making any psychiatric contact were born to parents with no history of any mental disorder. We were of course unable to examine familial risk beyond that indicated by parental mental disorder necessitating contact with mental health services.

Our findings may have implications for the validity of current diagnostic classification systems. Mental disorders continue to be largely defined on the basis of symptom clustering and, for some diagnoses, the impact of disorder on functioning. Efforts to delineate the causal and, in particular, biological underpinnings of individual disorders have been frustrated by the inadequacy of phenotypes defined in this way. Craddock and Owen[46] have recently called for an end to the dichotomous classification of psychosis on the basis of the growing evidence for a shared genetic basis for schizophrenia and bipolar disorder. We have certainly found that risk for mental disorder among offspring with parental history of disorder extends well beyond the boundaries of diagnoses based on the *ICD* system of classification. The existence of shared risk factors may, however, arguably be insufficient to reject clinically useful diagnostic categorizations.

Finally, we examined cumulative incidence rates for any psychiatric contact for male and female offspring during the follow-up period. All parental mental disorder exposure groups were found to be associated with elevated absolute risk (higher than that of the reference group) for offspring at all ages and for both sexes. The pattern of risk associated with particular exposure groups was similar for male and female offspring. Overall, cumulative incidence was higher among female offspring and this appeared to be true for all exposure groups.

Parental mental disorder confers an increased risk of mental disorder among offspring. The pattern of risk found in this study did not respect diagnostic boundaries, indicating either that risk was mediated by genetic and environmental factors that give rise to a general vulnerability to development of mental disorder and/or that our current diagnostic classification systems are lacking validity. We did find some evidence for concordance in risk and evidence of 2 dose-response relationships, the first relating to the number of affected parents and the second reflecting the greater risk associated with serious compared with other mental disorders in parents.

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