ORIGINAL ARTICLE

Prospective Study of Adult Mental Disturbance in Offspring of Women With Psychosis

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Background: The high-risk method is an important strategy for studying the antecedents and causes of schizophrenia and other psychoses. The Swedish High-Risk Project is a prospective longitudinal study of offspring of women with a history of schizophrenic, schizoaffective, affective, or unspecified functional psychoses and control women with no history of psychosis. The offspring and their environments were studied beginning before birth, and again during childhood. This article reports the mental outcome results from the first adult follow-up at age 22 years.

Methods: Of 178 offspring, 166 (93%) were followed up and blindly assessed using standardized methods, including a self-report scale for mental symptoms and the Structured Clinical Interview for *DSM-III-R*.

Results: Compared with controls (n=91), the offspring of mothers with schizophrenia (n=28) showed a significantly increased frequency of *DSM-III-R* Axis I and Axis II disorders, poor global functioning, high Symptom Checklist–90 scores, and a history of mental health care and psychopharmacologic medication use. Offspring of mothers with affective disorders (n=22) showed high Symptom Checklist–90 scores, more frequent poor functioning, and receipt of mental health care, with a significant increase in Axis I depressive disorders and no increase in Axis II disorders. The extension of schizophrenia and affective risk groups to include additional maternal "spectrum cases" (10 and 15 individuals, respectively) generally yielded similar results.

Conclusions: Maternal schizophrenia is associated with widespread increases in offspring mental disturbance in adolescence and young adulthood, differing from offspring disturbance associated with maternal affective disorder.

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SINCE THE 1950s, prospective longitudinal studies of individuals at heightened risk for future serious psychopathologic conditions have been considered a potentially valuable, if logistically demanding, strategy for studying the origins and development of such conditions.[1,2] The high-risk strategy is based on the fact that offspring born to parents with psychosis are at increased risk for the later development of psychosis and other forms of psychiatric illness. Whereas the lifetime risk of developing schizophrenia is approximately 1% in the general population, the risk is 10% to 15% in children with a parent with schizophrenia.[3,4] First-degree relatives of patients with affective psychoses (unipolar and bipolar combined) have shown a risk for similar disorders of 6% to 24%.[3,5-7] Risk of unipolar affective disorder is equally high in relatives of bipolar and unipolar groups, whereas risk of bipolar disorder is higher in relatives of patients with bipolar disorder. Relatives of patients with schizoaffective disorders have up to a 5% risk of schizoaffective disorders, and possibly an even higher risk of developing schizophrenialike disorders or bipolar disorder.[5-7] Relatives' risk of nonpsychotic unipolar affective disorder seems to be approximately equivalent across schizophrenic, schizoaffective, and affective diagnostic groups.[5]

To be effective in studying the antecedents of relevant psychiatric disorders, prospective high-risk studies need to follow the participants into adulthood. Few of the studies, begun in the 1970s[8-16] or later,[17] of groups at high risk for schizophrenia have succeeded in such follow-ups. Most high-risk studies[10-13] that have completed evaluation of psychopathologic disorders in the offspring of schizophrenic parents in late adolescence and adulthood found an increased occurrence of schizophrenia (6.7%-20.8%) and cluster A personality disorder (0%-50%) but, with one exception,[14] no increase in

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nonpsychotic affective disorders in the offspring. The offspring of parents with affective disorders have shown an increased rate of schizophrenia-related psychosis, cluster A personality disorder, anxiety disorders, and affective disorders.[13,18] The New York High-Risk Project also found heightened comorbidity (ie, >1 Axis I disorder) in offspring of mothers with schizophrenia and mothers with affective disorders.[13]

Further high-risk studies would make a contribution by (1) following individuals prospectively from the prenatal and perinatal period to adulthood and (2) comparing offspring mental disturbances associated with different types of maternal psychoses.

The Swedish High-Risk Project has attempted to make such a contribution. In 1973-1977, McNeil et al[1] began this prospective longitudinal investigation of high-risk offspring of women with schizophrenic, schizoaffective, affective, and unspecified functional psychoses and control offspring of women with no history of psychosis. The project was begun during the mothers' pregnancies, and the first adult follow-up of this sample has now been completed at about 22 years of age. The purpose of this article is to present findings concerning the mental health of these offspring in adolescence and young adulthood.

We hypothesized that compared with control offspring, the offspring of mothers with a history of schizophrenia and affective psychosis have significantly increased rates of *DSM-III-R* Axis I and Axis II disorders, as well as comorbidity, self-reported mental symptoms, poor global functioning, a history of mental health care and psychopharmacologic medication use, and accumulated signs of mental disturbance. We also studied whether extending schizophrenia and affective maternal cases to include those with broader, "spectrum-type" disorders would affect the mental disorder rates of offspring.

METHODS

SAMPLE

Heightened offspring risk for psychiatric illness was defined on the basis of a history of psychosis in the (index) mother, whereas normal risk was defined on the basis of absence of a psychosis history in the (control) mother and biological father. Both index and control mothers were selected from women registered at local prenatal clinics in a large geographic area of southwestern Sweden during 1973-1977.[1] Index women were identified by comparing the names of 53 540 pregnant women with a list of approximately 5800 women of childbearing age who had been admitted to psychiatric hospitals in the area and who had diagnoses suggestive of a psychosis. The criteria for acceptance into the maternal psychosis (index) group were (1) psychiatric hospitalization with a relevant hospital discharge diagnosis sometime prior to the pregnancy that took place during the project sampling period; (2) diagnosis by senior project diagnosticians (Lennart Kaij, MD, and Ann Malmquist-Larsson, MD) as representing a "nonorganic" psychosis, based on all known psychiatric records for the woman and, where relevant, her biological relatives; (3) identified in time to take part in the project prospectively from that pregnancy onward, and (4) spoke Swedish, Danish, or Norwegian.

This selection procedure identified 95 pregnant index cases with a fitting psychosis history; 88 (93%) accepted the invitation to participate in the project. The 88 cases represented 83 women, 5 of whom had 2 pregnancies during the project. This total index group was subdivided into 4 groups based on *Research Diagnostic Criteria*[19]: schizophrenia (Sc) (n=34), schizoaffective (Scaff) (n=15), affective (Aff) (n=27, with 18 bipolar and 9 unipolar depressive), and unspecified functional psychosis (Unsp) (n=12). None of the biological fathers of the high-risk fetuses had a history of hospitalization for psychosis.

One pregnant control woman was initially selected for each identified pregnant index woman. Controls were matched to index cases by prenatal clinic, maternal age (±1 year in 75% of cases and ±2 years in 25% of cases), parity (0, 1, and 2+), social class (upper, middle, and lower), and formal marital status in pregnancy, but controls did not have a history of hospitalization for psychosis in the woman herself or the fetus' biological father (as determined through medical records). Controls who again became pregnant during the selection period could participate twice, and controls who had already begun participation were studied even if the index case for whom they were chosen subsequently rejected participation or spontaneously aborted the pregnancy. In all, 106 controls were asked to participate, and 104 (98%) accepted (ie, 98 women, 6 of whom had 2 reproductions). The index and control maternal groups were considerably similar in age, parity, social class, and partnership status at the birth of the offspring.[1]

The offspring and their environments were studied extensively from before birth until age 2 years,[20] with follow-up and investigation at age 6 years[21] and at the present study age of about 22 years.

Fourteen (7.3%) of the original 192 cases who began participation during pregnancy withdrew from the study before the adult follow-up: 8 (1 Sc, 1 Aff, 2 Unsp, and 4 controls) during pregnancy (1 control owing to stillbirth), 3 (2 Aff and 1 control) soon after delivery, and the remaining 3 (1 Sc, 1 Aff, and 1 control) after the 6-year follow-up. Four of the 6 cases who terminated participation after delivery moved outside the project area (3 of these moved abroad).

Beginning in 1996, the remaining 178 offspring (80 high-risk individuals and 98 controls) were traced through the Swedish population registers and invited to participate in the young adult follow-up. The sample was contacted over a 4-year period to standardize age at this follow-up examination. Contact was made first by mail, followed by a telephone call. Of the 178 offspring invited to participate, 166 (93.3%) accepted. The rate of participation was equally high in the high-risk (75/80 or 94%) and control (91/98 or 93%) groups (**Table 1**). The young adult follow-up thus included 87% of the total 192 offspring (75/88 or 85% of offspring in the high-risk group and 91/104 or 88% of offspring in the control group) whose mothers originally began the study during pregnancy.

The maternal diagnostic grouping of participating high-risk offspring and the age and sex distributions of the high-risk and control groups are given in Table 1. Mean age at follow-up was identical (22.4 years) in the high-risk and control groups, with 88% and 87%, respectively, aged 22 to 24 years.

Owing to the small size of the Scaff and Unsp offspring groups, the psychiatric histories of the mothers were further evaluated (by both of us [E.W.S. and T.F.M.], independently and masked to offspring characteristics). Each maternal case was assigned to "mainly Sc" (n=10) or "mainly Aff" (n=15) disorders. The classification of Scaff cases was based on *Research Diagnostic Criteria for a Selected Group of Functional Disorders*, and Unsp cases were classified on the basis of predominant symptom pattern. Of the 15 Scaff cases, 7 were mainly Sc and 8 were mainly Aff; of the 10 Unsp cases, 3 were mainly Sc and 7 were mainly Aff. This reclassification was used to study the effect of extending Sc and Aff maternal groups to include additional "spectrum" cases.

The project was approved by the research ethics board of Lund University.

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Table 1. Demographic and Follow-up Data for 166 Offspring Who Participated in the Study

Variable	Participants: Contacted, No. (n = 178)	Participants: Followed Up, No. (%) (n = 166)	Age, Mean (SD), y	Range	Males, %
Control group	98	91 (93)	22.4 (1.0)	6	47
High-risk group					
Sc	32	28 (88)	22.5 (1.2)	6	71
Aff	23	22 (96)*	22.0 (1.3)	6	55
Scaff	15	15 (100)	22.5 (1.1)	3	53
Unsp	10	10 (100)	22.6 (1.4)	4	40
Subtotal	**80**	**75** (94)	22.4 (1.2)	6	59

Abbreviations: Aff, offspring of mothers with affective disorder; Sc, offspring of mothers with schizophrenia; Scaff, offspring of mothers with schizoaffective disorder; Unsp, offspring of mothers with unspecified functional psychosis.
*73% Bipolar mothers and 27% unipolar mothers.

PROCEDURE AND ASSESSMENTS OF OFFSPRINGS PSYCHIATRIC SYMPTOMS

Participants were followed up during a full day of assessment at their local general practitioners' offices, which provided a neutral environment in participants' own geographic areas. The standardized procedure during the morning session consisted of extensive neuropsychological testing, a neurological examination, and completion of self-report scales concerning mental health, life events, and familial and social environments. Diagnostic interviews based on *DSM-III-R* were conducted during the afternoon. The total day of examination yielded the opportunity to observe the participant's behavior in different situations. This standardized follow-up routine could not be followed for 3 participants. One control offspring had died of unknown causes after being contacted. The mother was interviewed in detail about the individual, and the diagnostic judgment was based on that information. Another control offspring who had infantile autism was still totally mentally handicapped in adulthood, and this previous diagnosis was used for this case. In the third case, a high-risk offspring had episodes of mental disturbance that hindered participation at follow-up. The diagnostic decision was based on telephone contact on several occasions and information from the psychiatric record.

All participants were assessed by one examiner (E.W.S.) with extensive psychiatric diagnostic experience. During the data collection and diagnostic decision phases, the examiner was uninformed as to the participant's group status and to all previous project data regarding the individual. Interrater reliability in diagnosis of psychiatric patients with various psychotic conditions was tested (with Richard Bernce, MD) before (n=5) and after (n=5) the present follow-up ($\kappa=1.0$; $P<.001$).

DSM-III-R Axis I and Axis II Diagnosis

The Swedish version of the Structured Clinical Interview for *DSM-III-R* was used to diagnose Axis I and Axis II disorders in the offspring.[22,23] Axis I disorders could occur at any time during adolescence and adulthood until follow-up. The Axis II personality disorders that were scored were those existing at the time of follow-up. Occurrence of Axis II personality disorders was calculated in terms of cluster A (paranoid, schizoid, and schizotypal), cluster B (antisocial, borderline, histrionic, and narcissistic), and cluster C (avoidant, dependent, obsessive-compulsive, and not otherwise specified) types. The 3 individuals who were diagnosed as having psychotic disorder were free of acute psychotic symptoms at the time of follow-up, which otherwise might have affected assessment of personality disorders. If any uncertainty about diagnosis occurred, the case was discussed with a senior psychiatrist.

Self-reported Mental Symptoms

The Symptom Checklist–90 (SCL-90)[24,25] was used to measure the participant's experience of mental symptoms during the past 14 days. The 90 self-report items represent 9 basic dimensions—psychoticism, paranoid ideation, interpersonal sensitivity, hostility, depression, anxiety, phobic anxiety, somatization, and obsessive-compulsive symptoms—plus a further dimension of "other symptoms" primarily reflecting eating and sleeping disturbance. The SCL-90 also yields a global severity index (sum of all points). A score greater than the 90th percentile of the scores for the controls was operationally defined as deviant.

Global Functioning and Receipt of Mental Health Care and Medication

Information about the participant's global functioning (psychologically, socially, and occupationally) was obtained through the Structured Clinical Interview for *DSM-III-R* and was scored using the Global Assessment of Functioning Scale.[26] A score of 70 or less was operationally defined as demarcating poor global functioning.

The Structured Clinical Interview for *DSM-III-R* also provided information about participants' receipt of any form of mental health care (from school or community psychologists, social workers, pediatricians, or psychiatrists) and use of psychopharmacologic medications such as antidepressives, neuroleptics, anxiolytics, and sleep medicine during adolescence and adulthood.

STATISTICAL METHODS

The Sc and Aff offspring groups were compared with the control group on the measures of mental disturbance described in previous sections using the Fisher exact probability, with odds ratios and 95% confidence intervals. As suggested by the hypotheses, 1-tailed tests were used. The level of significance was set at $P\leq.05$, with $.10\geq P>.05$ denoting nonsignificant trends.

The rates of mental disorders for Scaff and Unsp offspring are given in tabular form for descriptive purposes but were not submitted to formal statistical comparison with controls owing to small sample sizes. Instead, the Scaff and Unsp mothers were recategorized as representing mainly Sc or mainly Aff and were subsequently added to the Sc and Aff groups in

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Table 2. Adolescent and Adult Axis I and Axis II Disorders in High-Risk (n = 75) and Control (n = 91) Offspring[a]

Disorder	Controls (n = 91)	Sc (n = 28)	Aff (n = 22)	Scaff (n = 15)	Unsp (n = 10)	Sc Spect (n = 38)	Aff Spect (n = 37)
Current Axis I disorder	13 (14)	4 (14)	5 (23)	5 (33)	2 (20)	6 (16)	10 (27)
Lifetime Axis I disorder	21 (23)	15 (54)[b]	9 (41)[l]	5 (33)	6 (60)	19 (50)	16 (43)
>1 Axis I disorder	7 (8)	7 (25)[c]	4 (18)	3 (20)	2 (20)	8 (21)	8 (22)
Any psychotic disorder	0	2 (7)[d]	0	1 (7)	0	3 (8)	0
Any depressive disorder	11 (12)	12 (43)[e]	9 (41)[m]	4 (27)	4 (40)	15 (39)	14 (38)
Any anxiety disorder	12 (13)	3 (11)	5 (23)	3 (20)	0	3 (8)	8 (22)
Any eating disorder	2 (2)	1 (4)	0	1 (7)	0	1 (3)	1 (3)
Any substance abuse disorder	3 (3)	7 (25)[f]	2 (9)	0	3 (30)	7 (18)	5 (14)
Autistic disorder	1 (1)	0	0	0	0	0	0
Any Axis II disorder(s)	11 (12)	12 (43)[g]	5 (23)	4 (27)	6 (60)	18 (47)	9 (24)
>1 Axis II disorder	0	4 (14)[h]	1 (5)	2 (13)	0	5 (13)	2 (5)
Cluster A (≥1)	2 (2)	3 (11)[i]	1 (5)	3 (20)	2 (20)	7 (18)	2 (5)
Cluster B (≥1)	3 (3)	3 (11)	3 (14)[n]	2 (13)	1 (10)	3 (8)	6 (16)
Cluster C (≥1)	6 (7)	11 (39)[j]	2 (9)	1 (7)	3 (30)	14 (37)	3 (8)
Axis I and Axis II disorders	6 (7)	8 (29)[k]	6 (27)[o]	1 (7)	3 (30)	11 (29)	7 (19)

Abbreviations: Aff, offspring of mothers with affective disorder; Aff spect, offspring of mothers with psychosis in affective spectrum; CI, confidence interval; OR, odds ratio; Sc, offspring of mothers with schizophrenia; Scaff, offspring of mothers with schizoaffective disorder; Sc spect, offspring of mothers with psychosis in schizophrenia spectrum; Unsp, offspring of mothers with unspecified functional psychosis.

[a]Data are given as number (percentage). Statistical analysis: controls vs Sc and controls vs Aff only. *P* value by the Fisher exact test (1-tailed); OR (95% CI).
[b]Controls vs Sc: *P* = .003; 3.85 (1.58-9.35).
[c]Controls vs Sc: *P* = .02; 4.00 (1.26-12.66).
[d]Controls vs Sc: *P* = .05; 17.26 (0.80-371.07).
[e]Controls vs Sc: *P*<.001; 5.45 (2.05-14.51).
[f]Controls vs Sc: *P* = .002; 9.78 (2.33-41.03).
[g]Controls vs Sc: *P*<.001; 5.45 (2.05-14.52).
[h]Controls vs Sc: *P* = .003; 33.61 (1.75-646.25).
[i]Controls vs Sc: *P* = .08; 5.34 (0.85-33.75).
[j]Controls vs Sc: *P*<.001; 9.17 (2.98-28.18).
[k]Controls vs Sc: *P* = .004; 5.67 (1.77-18.18).
[l]Controls vs Aff: *P* = .08; 2.31 (0.87-6.15).
[m]Controls vs Aff: *P* = .004; 5.03 (1.74-14.51).
[n]Controls vs Aff: *P* = .09; 4.63 (0.87-24.75).
[o]Controls vs Aff: *P* = .01; 5.31 (1.52-18.57).

secondary analyses to determine possible effects on the rates of offspring disorders.

RESULTS

SCHIZOPHRENIA AND AFFECTIVE RISK GROUPS VS CONTROLS

Axis I Disorders

Compared with controls, Sc offspring showed significantly higher frequencies of 1 or more adolescent or adult Axis I disorders, comorbidity on Axis I disorders, depressive disorders, and substance abuse disorders, with a trend toward more psychotic disorders (**Table 2**). In contrast, Aff offspring showed a significantly higher frequency of depressive disorders only, with a trend toward more adolescent or adult Axis I disorders in total. The cases of schizophrenia (n=1) and manic psychotic episode (n=1) occurred among Sc offspring, and the case of schizoaffective disorder occurred among Scaff offspring. As found earlier, the single case of infantile autism, with continued severe disability in adulthood, occurred in the control group.

Axis II Disorders

Compared with controls, Sc offspring showed significantly higher frequencies of Axis II disorders of any type, 1 or more cluster C personality disorders, and comorbidity on personality disorders, with a trend toward more cluster A personality disorders (Table 2). The Aff offspring showed only a nonsignificant trend toward more cluster B personality disorders. The co-occurrence of Axis I and Axis II disorders was significantly increased in Sc and Aff offspring vs controls. Examples of such Axis I and II combinations are (1) depression and antisocial personality disorder or borderline personality disorder and (2) eating disorder and borderline personality.

Self-reported Mental Symptoms

Significantly more of the Sc offspring scored above the control group's 90th percentile cutoff level on the SCL-90 general severity index and the psychoticism, interpersonal sensitivity, and phobic anxiety subscales, with a similar trend for anxiety (**Table 3**). Significantly more Aff offspring scored high on the general severity index, phobic anxiety, and other symptoms (eg, sleep disturbance), with similar trends for increased interpersonal sensitivity, depression, and anxiety.

Global Functioning and Receipt of Mental Health Care and Medication

Significantly higher proportions of Sc and Aff offspring (vs controls) had Global Assessment of Functioning Scale scores

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Table 3. Offspring Scoring Above the Control Group's 90th Percentile on the SCL-90*

Symptom Dimension	Controls (n = 88)	Sc (n = 28)	Aff (n = 22)	Scaff (n = 15)	Unsp (n = 9)	Sc Spect (n = 38)	Aff Spect (n = 36)
General severity index	8 (9)	7 (25)†	7 (32)†	2 (13)	2 (22)	9 (24)	10 (28)
Psychoticism	7 (8)	7 (25)†	3 (14)	2 (13)	3 (33)	10 (26)	5 (14)
Paranoid ideation	6 (7)	4 (14)	3 (14)	2 (13)	2 (22)	6 (16)	5 (14)
Interpersonal sensitivity	8 (9)	7 (25)†	5 (23)‡	4 (27)	1 (11)	9 (24)	8 (22)
Hostility	8 (9)	5 (18)	4 (18)	4 (27)	3 (33)	7 (18)	9 (25)
Depression	7 (8)	4 (14)	5 (23)‡	4 (27)	1 (11)	6 (16)	8 (22)
Anxiety	8 (9)	6 (21)‡	5 (23)‡	2 (13)	2 (22)	8 (21)	7 (19)
Phobic anxiety	8 (9)	7 (25)†	6 (27)†	3 (20)	2 (22)	9 (24)	9 (25)
Somatization	7 (8)	3 (11)	3 (14)	2 (13)	2 (22)	5 (13)	4 (11)
Obsessive-compulsive	7 (8)	4 (14)	2 (9)	1 (7)	2 (22)	6 (16)	3 (8)
Other (sleep disturbance. . .)	6 (7)	3 (11)	5 (23)†	1 (7)	3 (33)	5 (13)	7 (19)

Abbreviations: Aff, offspring of mothers with affective disorder; Aff spect, offspring of mothers with psychosis in affective spectrum; Sc, offspring of mothers with schizophrenia; Scaff, offspring of mothers with schizoaffective disorder; SCL-90, Symptom Checklist–90; Sc spect, offspring of mothers with psychosis in schizophrenia spectrum; Unsp, offspring of mothers with unspecified functional psychosis.

*Data are given as number (percentage).

†Controls vs Sc and controls vs Aff only: Fisher exact $P<.05$, 1-tailed.

‡Controls vs Sc and controls vs Aff only: Fisher exact $P<.10$, 1-tailed.

Table 4. Poor Global Functioning, Receipt of Mental Health Care, and Medication Use*

Variable	Controls (n = 89)	Sc (n = 28)	Aff (n = 22)	Scaff (n = 15)	Unsp (n = 10)	Sc Spect (n = 38)	Aff Spect (n = 37)
GAFS score ≤70	6 (7)	12 (43)†	5 (23)‖	7 (47)	5 (50)	17 (45)	12 (32)
Mental health care	10 (11)	14 (50)‡	7 (32)¶	6 (40)	4 (40)	18 (47)	13 (35)
Medication	4 (4)	5 (18)§	2 (9)	3 (20)	0	6 (16)	4 (11)

Abbreviations: Aff, offspring of mothers with affective disorder; Aff spect, offspring of mothers with psychosis in affective spectrum; CI, confidence interval; GAFS, Global Assessment Functioning scale; OR, odds ratio; Sc, offspring of mothers with schizophrenia; Scaff, offspring of mothers with schizoaffective disorder; Sc spect, offspring of mothers with psychosis in schizophrenia spectrum; Unsp, offspring of mothers with unspecified functional psychosis.

*Data are given as number (percentage). Statistical analysis: controls vs Sc and controls vs Aff only. *P* value by the Fisher exact test (1-tailed); OR (95% CI).

†Controls vs Sc: $P<.001$; 10.38 (3.40-31.70).

‡Controls vs Sc: $P<.001$; 7.90 (2.93-21.28).

§Controls vs Sc: $P = .04$; 4.62 (1.15-18.61).

‖Controls vs Aff: $P = .04$; 4.07 (1.11-14.88).

¶Controls vs Aff: $P = .02$; 3.69 (1.21-11.22).

describing poor functioning (≤70 points) (**Table 4**). Participant reports of having received mental health care at some time during adolescence or adulthood (from school or community psychologists, social workers, pediatricians, or psychiatrists) were significantly more frequent in Sc and Aff offspring vs controls (Table 4). The highest rate was found in Sc offspring, 50% of whom had received some form of mental health care. Having received antidepressive, neuroleptic, anxiolytic, or sleep medicines at some time during adolescence or adulthood was also significantly more frequent in Sc offspring vs controls (Table 4).

Accumulated Signs of Mental Disturbance During Adolescence and Adulthood

Our a priori operational measure of accumulated signs of mental disturbance represented Axis I diagnoses in adolescence or adulthood (step A), with stepwise additions of current Axis II diagnoses (step B), greater than 2 criteria for *DSM-IV* personality disorders in any given cluster (step C), and, finally, having received mental health care during adolescence or adulthood (step D).

Significantly more Sc offspring than controls were at each of the 4 aggregation steps (**Table 5**). By step D, these signs of mental disturbance were shown by 89% of Sc offspring vs 39% of controls. The Sc offspring showed markedly increasing differences (odds ratios) from controls as further signs of mental disturbance were added in (ie, progressing from step A to step D).

In contrast, Aff offspring did not differ significantly from controls at any of the 4 steps, and the odds ratios remained stable or even decreased as further signs of mental disturbance were accumulated from step A to step D.

SCHIZOPHRENIA RISK AND AFFECTIVE RISK SPECTRA

The mental health characteristics of the Scaff and Unsp offspring groups are given in Tables 2 through 5. The Scaff offspring were most similar to Aff offspring, and Unsp offspring were generally similar to Sc offspring on many of the mental characteristics (eg, total Axis I and Axis II disorders, anxiety and substance abuse disorders, and cluster C personality disorders).

This result changed somewhat when Scaff and Unsp maternal cases were reassigned to schizophrenia vs affective spectra. The addition of these cases to the origi-

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Table 5. Accumulated Signs of Mental Disturbance*

	Step A	Step B	Step C	Step D
Controls, %	23	28	37	39
Sc (vs controls)†				
%	54	68	78	89
P value	.003	<.001	<.001	<.001
OR	3.85	5.28	6.22	12.86
95% CI	1.58-9.35	2.11-13.17	2.29-16.92	3.61-45.84
Aff (vs controls)†				
%	41	41	45	55
P value	.08	.19	.31	.15
OR	2.31	1.73	1.41	1.85
95% CI	0.87-6.15	0.66-4.54	0.55-3.63	0.72-4.74
Scaff (vs controls)				
%	33	47	67	67
OR	1.67	2.19	3.39	3.09
95% CI	0.51-5.42	0.72-6.65	1.07-10.79	0.97-9.79
Unsp (vs controls)				
%	60	90	90	100
OR	5.00	22.5	13.58	29.17
95% CI	1.29-19.41	2.71-186.7	1.62-113.49	1.64-517.43
Sc spect (vs controls)				
%	50	66	79	87
OR	3.33	4.81	6.36	10.18
95% CI	1.49-7.43	2.14-10.81	2.61-15.5	3.63-28.59
Aff spect (vs controls)				
%	43	51	56	64
OR	2.54	2.64	2.12	2.73
95% CI	1.13-5.73	1.20-5.81	0.97-4.65	1.22-6.09

Abbreviations: Aff, offspring of mothers with affective disorder; Aff spect, offspring of mothers with psychosis in affective spectrum; CI, confidence interval; OR, odds ratio; Sc, offspring of mothers with schizophrenia; Scaff, offspring of mothers with schizoaffective disorder; Sc spect, offspring of mothers with psychosis in schizophrenia spectrum.

*Step A, Axis I; step B, Axis I and/or II; step C, Axis I and/or II and/or greater than 2 personality disorder criteria in any cluster; step D, Axis I and/or II and/or greater than 2 personality disorder criteria in any cluster and/or received mental health care.

†Controls vs Sc and controls vs Aff only: *P* value by the Fisher exact test (1-tailed).

nal Sc and Aff groups, to form extended "schizophrenia risk" and "affective risk" spectra, resulted in findings that were generally similar to those for the original Sc and Aff offspring groups (Tables 2-5). All 3 psychoses were included in the Sc spectrum, and the rate of cluster A personality disorders increased in the Sc spectrum group (vs the Sc group). The 2 notable changes regarding Aff risk were the increases in poor global functioning (Table 4) and in accumulated signs of mental disturbance (Table 5) in Aff spectrum offspring (vs Aff offspring). The change in accumulated signs was primarily due to an increase in personality disorders (at step B) in Aff spectrum offspring.

COMMENT

This prospective longitudinal study of young adults is unique among longitudinal high-risk studies in that it began before the participants' births for purposes of charting future serious psychopathologic conditions. This follow-up in young adulthood found that Sc offspring showed high rates of mental disturbance, with increases in adolescent and adult Axis I disorders, depressive disorders, substance abuse disorders, Axis II disorders, various types of comorbidity, and self-reported symptoms of psychoticism, interpersonal sensitivity, and phobic anxiety.

The Aff offspring showed a less distinct picture of mental disturbance. Although only Axis I depressive disorders were increased in this group (vs controls), the group showed increased rates of high scores for the SCL-90 general severity index, phobic anxiety, and "other" symptoms; poor global functioning; and increased receipt of mental health care.

The current Aff offspring group included mothers with bipolar disorder (n=16) and mothers with unipolar affective disorders (n=6). In contrast to some previous research,[7,18] the offspring of bipolar mothers tended to have more mental disturbance, for example, more Axis I diagnoses (7 of 16 offspring of bipolar mothers vs 2 of 6 offspring of unipolar mothers), Axis II diagnoses (4 of 16 offspring of bipolar mothers vs 1 of 6 offspring of unipolar mothers), poor global functioning (5 of 16 offspring of bipolar mothers vs 0 of 6 offspring of unipolar mothers), and receipt of mental health care (7 of 16 offspring of bipolar mothers vs 0 of 6 offspring of unipolar mothers).

Of 75 high-risk participants, only 3 (4%) had psychosis (1 case of schizophrenia and 1 case of manic psychotic episode [2/28 or 7%] among Sc offspring and 1 case of schizoaffective disorder [1/15 or 7%] among Scaff offspring). This is a relatively low rate of psychosis compared with that in other family and high-risk studies,[3-5,9-14] which may be explained by the fact that the offspring have passed through only part of their lifetime risk. Additional cases of psychosis could in theory also be found among the few nonparticipants (7% high risk and control). The severity of maternal illness or the sample selection procedure may also differ from that used in other studies.

Despite the low rate of psychoses, a high rate of total psychiatric disturbance was identified in the high-risk groups (Table 5). The increased rate of adolescent or adult depressive disorders (approximately 40%) was almost equal in frequency among the Sc and Aff offspring groups. Although this is at variance with findings from the Copenhagen High-Risk Project,[11] an increased rate of depressive disorders has been found in other studies[14,27] of first-degree relatives of schizophrenic patients. The current observations of depression might represent a prodromal symptom of future psychotic disorder.[28,29] Depression might also be an appropriate psychic response to having grown up in environments characterized by maternal psychosis rather than a result of genetic influence.[30]

The observed increase in substance abuse disorders among offspring of mothers with schizophrenia but not affective psychosis fits well with some,[11] but not all,[13,30-32] previous studies. Psychiatric risk seems to yield increased vulnerability to substance abuse, but the manifestation of mental vulnerability in this form may well depend on the drug culture norms in the particular study setting.

The Sc offspring showed elevated rates of cluster C personality disorders, with a similar tendency for cluster A personality disorders. This finding is consistent with previous findings from studies[11,12,30,32-38] in which relatives of schizophrenic patients had increased rates of schizoid, schizotypal, and paranoid personality disorders (clus-

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ter A disorders) and, in some studies, avoidant personality disorder. In contrast, we did not confirm previous findings[12] of such disorders among Aff offspring.

The similarities in mental disturbance between Sc and Unsp offspring and between Aff and Scaff offspring could possibly suggest a common etiologic origin for these pairs of psychoses. Nevertheless, about half of the Scaff mothers were clinically classified as being mainly Sc, whereas most (7 of 10) of the Unsp mothers were classified as being mainly affective in symptom picture. The spectrum approach of extending Sc and Aff groups to include other mainly Sc spectrum and mainly Aff spectrum cases seems to represent a promising approach to increasing sample size without unduly affecting offspring mental disturbance rates (at least in this data set). The general similarity of results in original Sc and Aff vs Sc spectrum and Aff spectrum risk samples might suggest that whatever factors are affecting the offspring mental disturbance rates, these factors are equally manifest in the additional risk spectrum cases and in the original cases. Almost all (10 of 12) of the Sc spectrum–related disorders in the offspring (ie, the 3 psychosis cases and 7 of the 9 cluster A personality disorders) followed the mothers' Sc spectrum diagnoses, reminiscent of findings in the New York High-Risk Study.[12]

The strengths of the study are the prospective design, the high adult follow-up rate, the narrow age range at examination, the standardized examination routine conducted in person by a single trained investigator who was masked to the participant's study group and previous project data, and the existence of different high-risk groups.

The limitations of this study are the small sample sizes of the specific high-risk groups (yielding low statistical power), the fact that diagnostic judgments for offspring could not be independently confirmed (eg, by independent assessments of videotapes of the diagnostic interviews), and the fact that the participants have only passed through part of their lifetime risk for Axis I disorders.

The investigation of Axis I disturbance "existing sometime during adolescence or adulthood" identified 2 to 3 times as much disturbance as the point prevalence approach (disturbance existing on the day of assessment) and has considerably more relevance in a high-risk study of mental outcome. Extensive overlap was observed between current Axis I diagnoses and all 10 self-reported SCL-90 symptom dimensions, supporting the validity of the clinical decision.

The risk groups were heterogeneous with respect to sex, with the Sc offspring group having a higher proportion of males (71%) compared with the other groups (Table 1). This had no effect on the results, as no sex difference was found within the Sc offspring group regarding the mental outcome variables.

Five index families and 6 control families each had 2 different offspring participating in the adult follow-up. No intrafamilial statistical dependency occurred regarding mental outcome.

A high rate of accumulated signs of mental disturbance, defined according to our a priori model, was especially abundant among Sc offspring: 89% of these offspring had 1 or more signs of mental disturbance. Our results confirm that maternal psychosis, and definitely schizophrenia, plays an important role in the mental health of offspring in young adulthood. The effect of maternal affective disorder seems to be quite different. The early signs of and background reasons for offspring mental disturbance will be the focus of our continued work using the prospectively recorded data for this sample.

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