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# Risk of Mental Illness in Offspring of Parents With Schizophrenia, Bipolar Disorder, and Major Depressive Disorder: A Meta-Analysis of Family High-Risk Studies

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***Objective:*** **Offspring of parents with severe mental illness (SMI; schizophrenia, bipolar disorder, major depressive disorder) are at an increased risk of developing mental illness. We aimed to quantify the risk of mental disorders in offspring and determine whether increased risk extends beyond the disorder present in the parent.** ***Method:*** **Meta-analyses of absolute and relative rates of mental disorders in offspring of parents with schizophrenia, bipolar disorder, or depression in family high-risk studies published by December 2012.** ***Results:*** **We included 33 studies with 3863 offspring of parents with SMI and 3158 control offspring. Offspring of parents with SMI had a 32% probability of developing SMI (95% CI: 24%–42%) by adulthood (age >20). This risk was more than twice that of control offspring (risk ratio [RR] 2.52; 95% CI 2.08–3.06, $P < .001$). High-risk offspring had a significantly increased rate of the disorder present in the parent (RR = 3.59; 95% CI: 2.57–5.02, $P < .001$) and of other types of SMI (RR = 1.92; 95% CI: 1.48–2.49, $P < .001$). The risk of mood disorders was significantly increased among offspring of parents with schizophrenia (RR = 1.62; 95% CI: 1.02–2.58; $P = .042$). The risk of schizophrenia was significantly increased in offspring of parents with bipolar disorder (RR = 6.42; 95% CI: 2.20–18.78, $P < .001$) but not among offspring of parents with depression (RR = 1.71; 95% CI: 0.19–15.16, $P = .631$).** ***Conclusions:*** **Offspring of parents with SMI are at increased risk for a range of psychiatric disorders and one third of them may develop a SMI by early adulthood.**

*Key words:* schizophrenia/bipolar disorder/depression/offspring/meta-analysis

## Introduction

Offspring of parents with severe mental illness (SMI; schizophrenia, bipolar disorder, major depressive disorder) have an increased risk of developing a mental illness themselves.[1–4] Individuals with SMI want to know the probability that their offspring will develop SMI. Accurate quantification of risk is an important element in communication with patients and their families.[5–7] Knowing the probability of illness in offspring is also crucial for the planning of early interventions.

Family high-risk (FHR) studies investigate psychopathology in individuals who have a biological relative, most commonly a parent, with SMI. These studies have provided a wealth of information about risk of mental disorders in offspring. However, the rates of mental disorders in offspring vary across studies, and a robust overall estimate is not available.

Most FHR studies have primarily focused on the risk of developing the same disorder as the parent suffered from; eg, schizophrenia among offspring of parents with schizophrenia. Several FHR studies have reported that familial risk was diagnosis specific, eg, children of parents with schizophrenia were at increased risk for nonaffective psychosis but not for mood disorders.[8–10] However, evidence emerging from population registry studies suggests that familial risk might be broader, with children of parents with SMI also having increased risk for mental disorders other than the disorder diagnosed in the parent.[2] Such nonspecific risks are supported by twin and molecular genetic studies showing that genetic dispositions to mood disorders and schizophrenia overlap.[11–13] If these results are confirmed, the overall risk of psychopathology in offspring of parents with SMI may be higher than previously thought.

There are 2 alternative explanations for the discrepant findings of population registry and FHR studies. It may be that the familial risk is diagnosis specific, but

the findings of population registry studies are distorted by misclassification due to lack of valid diagnostic instruments.[14,15] Alternatively, it may be that familial risk cuts across diagnoses, but individual FHR studies might have been underpowered to detect the cross-diagnostic risks. To distinguish between these alternative explanations we conducted a meta-analysis of FHR studies. This retains the advantage of valid diagnostic interviews in FHR studies while the statistical power is increased through pooling of data across studies. We aimed to quantify the risk of a range of mental disorders among the offspring of individuals with schizophrenia, bipolar disorder, and major depressive disorder.

## Methods

### *Inclusion Criteria*

We included published cross-sectional and longitudinal studies of biological offspring of parents with SMI. We defined SMI as psychotic or major mood disorder (schizophrenia, schizophreniform psychosis, psychotic disorder not otherwise specified, schizoaffective disorder, bipolar disorder, major depressive disorder). Offspring were grouped by parental diagnosis: (1) schizophrenia (schizophrenia, schizophreniform disorders, nonaffective psychosis), (2) bipolar disorder, and (3) depression. In addition, there was a small number of offspring of parents with a diagnosis of schizoaffective disorder. Because schizoaffective disorder shares features with both schizophrenia and bipolar disorder, we excluded these offspring from analyses concerning specificity of familial risk.

Study inclusion criteria are summarized in box 1. To minimize selection bias from offspring psychopathology and help-seeking behavior, we excluded studies that recruited offspring presenting to services, relied on registry diagnoses, or excluded offspring with psychopathology at baseline. We included studies that systematically assessed offspring with a valid diagnostic interview at mean age of 10 years or higher. We did not include studies of children under 10 years because most disorders of interest have onset at higher age.

### *Search Strategy*

We searched MEDLINE/PubMed, Embase, and PsycINFO for articles quantifying rates of mental illness in the offspring of individuals with SMI using combinations of search terms for mental disorders (mental disorder, mental disease, depression, bipolar, schizophrenia, psychosis) and offspring (child of impaired parents, family history, adult child, high risk, offspring, parental history), published by December 31, 2012. We perused bibliographies of identified articles for additional references. Eligibility was assessed by 2 authors (D.R. and R.U.) who met to come to a consensus on inclusion based on a priori criteria (box 1).

**Box 1. Study Inclusion Criteria**

- Parent diagnosis of severe mental illness (psychosis or major mood disorder).
- Offspring recruited through parents only; no exclusion or inclusion based on offspring psychopathology.
- Offspring systematically assessed at mean age 10 or higher with a valid diagnostic interview.

### *Data Extraction*

Two authors (D.R. and R.U.) extracted data from eligible articles: study year, author, region of study origin, sex, mean age, and age range of high-risk group and controls, number of follow-ups, parental diagnoses, methods of diagnosis in parents and offspring, blinding of child assessors to parent diagnosis (as reported in primary publications; assumed lack of blindness if not reported), method of recruitment and control group type (unscreened vs screened parents). Lifetime rates of the following diagnoses in offspring were recorded: schizophrenia, any nonaffective psychosis/schizophrenia spectrum disorders, bipolar disorder (I or II), major depressive disorder, any affective disorder, obsessive-compulsive disorder, panic disorder, social phobia, generalized anxiety disorder, separation anxiety, specific phobia, any anxiety disorder, attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder, conduct disorder, any disruptive behavior disorder, substance use disorder and any mental disorder. The range of offspring diagnoses was limited by what was available in the primary publications. Other diagnoses of interest, eg, autism spectrum disorders and personality disorders, were not reported in a sufficient number of studies to enable meta-analysis. When multiple assessments or time-frames for diagnoses were reported, we chose the lifetime or cumulative rate from the last reported assessment. We resolved inconsistencies in consensus meetings and contacted authors to provide additional data.

### *Outcome Definitions*

SMI in offspring was defined as schizophrenia or nonaffective psychosis, bipolar disorder (I or II) or major depressive disorder. Because the definitions of bipolar spectrum and minor depression are broad, these conditions were not counted as SMI. To test whether familial risk extends beyond the disorder diagnosed in the parent, we also defined "other SMI" as a psychotic or major mood disorder different from the diagnosis of the parent of the high-risk offspring (eg, if the parent of high-risk offspring had schizophrenia, other SMI was defined as bipolar or major depressive disorder). "Any mental disorder" was defined as SMI or anxiety disorder (generalized anxiety disorder, panic disorder, social phobia, obsessive-compulsive disorder, simple phobia or separation anxiety disorder), disruptive disorder (oppositional defiant disorder, conduct disorder, antisocial

personality disorder), ADHD or alcohol or substance use disorder in studies where overlap was specified so that rates were not inflated by comorbidity.

### *Meta-analysis*

Meta-analysis was performed using the suite of programs available through Stata.[16,17] We selected raw absolute rates and risk ratios (RR) as the measures of effect size because they are less prone to misinterpretation than odds ratios.[18–20] Raw rates of mental illness were first synthesized in high-risk offspring and then compared against matched control offspring in studies with control groups, using the program metan.[16] Heterogeneity between studies was tested with Cochran's $Q$.[21] Because significant heterogeneity was present in many analyses, random-effects estimates are presented, based on the DerSimonian and Laird method that incorporates between-study variance both into the study weights and into the SEs of the overall estimate.[22] We tested effects of study and sample characteristics, including offspring age at assessment, parent diagnosis, and blinding of child assessors to parent's diagnosis, using metaregressions.[21] We visualized the relationship between effect size and SE in funnel plots,[23] and we tested for small study bias using the Peter's test based on weighted linear regression of effect estimates on the reciprocal of the sample size.[24] Results are presented as absolute rates and RR with 95% CI. RR were determined by dividing the lifetime prevalence of a mental disorder in high-risk offspring by the prevalence in controls. The meta-analysis has both a hypothesis testing and descriptive purpose. The hypothesis that familial risk extends beyond diagnostic boundaries was tested with a single primary test comparing the risk of other SMI in FHR offspring against comparison offspring. Diagnosis-specific estimates serve a primarily descriptive purpose. Therefore, we consider a $P < .05$ as statistically significant without corrections for multiple testing. All $P$ values are 2 sided.

## Results

### *Description of Extracted Data*

The literature search identified 3962 articles. Additional 9 publications were found by searching bibliographies. Eventually, 33 studies satisfied all inclusion criteria (see figure 1 for reasons for exclusion and supplementary table 1 for description of included studies).

From the 33 included studies, we extracted information on 3863 offspring of parents with SMI. There were 874 offspring of parents with schizophrenia and related psychotic disorders, 1492 offspring of parents with bipolar disorder, and 1482 offspring of parents with major depressive disorder. In addition, there were 15 offspring of a parent with schizoaffective disorder. Twenty-five studies included information on 3158 control offspring matched on demographic variables to offspring of parents with SMI.

### *Role of Offspring Age*

The mean age of offspring of parents with SMI at the time of the last diagnostic assessment was 21.3 (SD 10.8) and differed by parent diagnosis: offspring of parents with schizophrenia and related disorders were on average 33.9 year old (SD 10.2); offspring of parents with bipolar disorder and major depressive disorder were on an average 17.9 (SD 8.6) and 17.2 (SD 6.7) year old.

We explored the effect of offspring age on psychopathology to determine the best strategy of accounting for age in the meta-analysis. A metaregression showed that the probability of SMI in FHR offspring significantly depended on age ($b = .040$, 95% CI 0.013–0.067, $P = 0.0175$). While the rate increased from adolescence to early adulthood, the effect of age was negligible among studies of offspring aged 20 or over ($b = .003$, 95% CI −0.075–0.080, $P = .948$). Unlike absolute risk, the RR of SMI in offspring of parents with SMI compared with control offspring did not significantly depend on age ($b = -.01$, 95% CI −0.03–0.01, $P = .229$). Regarding specific diagnoses, age of offspring was significantly positively associated with rates of schizophrenia ($b = .049$, 95% CI 0.010–0.088, $P = .0442$) but not bipolar disorder, depression, anxiety, disruptive or substance use disorders (all $P > .05$). ADHD was more common among studies of younger offspring ($b = -.113$. 95% CI −0.193 to −0.344, $P = .022$). Schizophrenia was no longer affected by age in studies of offspring aged 20 or over. ADHD was no longer affected by age among studies of offspring with mean age under 20. Therefore, we stratified all analyses by mean age of offspring at the last assessment (under 20, 20 years or over).

We also examined the effect of age difference between high-risk and control offspring. In most studies, high-risk and control offspring were tightly matched on age (average age of high-risk and control offspring within 1 year of each other in 21 of the 25 studies with control groups). Age difference did not significantly modify the RR, but there was a trend (−0.43, 95% CI −1.01–0.14, $P = .133$) and the largest RR was obtained in the study by Duffy and colleagues, which had the largest age difference between high-risk and control offspring. Therefore, we restricted the analyses of RR to the 22 studies where mean ages of high-risk and control offspring were within a year of each other.

### *Influence of Publication Bias and Study Characteristics*

We next explored the data for indications of small study bias. For absolute rates of SMI in offspring, funnel plots indicated no small study bias (supplementary figure 1A and B ). For relative rates of SMI in high-risk vs control offspring, funnel plots showed several smaller studies with larger RR. Supplementary figure 1 shows that these were studies of young offspring (under 20) of parents with bipolar disorder and depression. The Peter's test found no evidence for small study bias ($t = .66$, $P = .520$).

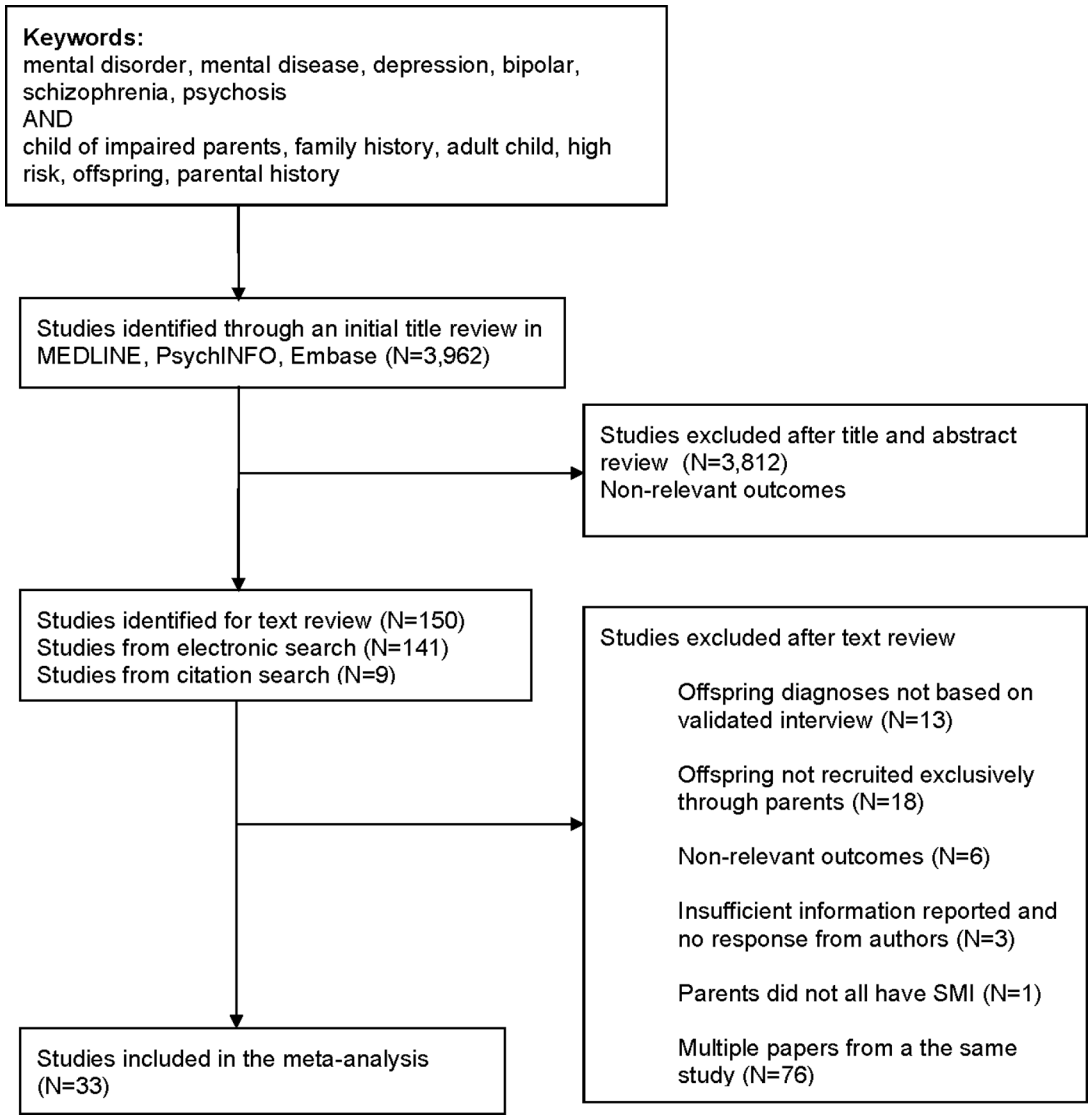


**Fig. 1.** Literature search results and study eligibility for meta-analysis of rates of mental disorders in offspring of individuals with severe mental illness (SMI).

We next tested the influence of relevant study characteristics on absolute and relative rates of psychopathology in offspring using metaregressions. Higher number of follow-up assessments was associated with higher absolute rates of disorders in offspring of parents with SMI ($b$ = .151, 95% CI 0.006–0.295, $P$ = .042); it did not affect relative rates in high-risk vs comparison offspring. Publication year, region of study origin, assessor blinding, duration of follow-up and type of control group did not influence results (all $P > .05$).

### *SMI in Offspring of Parents With SMI*

We first quantified the probability that an offspring of a parent with SMI develops any SMI, ie, schizophrenia or related psychotic disorder, bipolar disorder, or major depressive disorder. Effect of parental diagnosis on probability of SMI in offspring was not significant ($F(2,31) = .46$; $P = .635$). Therefore we first jointly analyzed studies of offspring of parents with any SMI. A random-effects meta-analysis of offspring aged 20 or more estimated that the probability of offspring of parents with SMI developing SMI themselves was 0.32 (95% CI 0.24–0.42), taking into account significant between-study heterogeneity ($Q = 188$, $df = 15$; $P < .001$). The probability of SMI among adolescent offspring (age 10–19) was 0.18 (95% CI 0.14–0.24), taking into account significant heterogeneity (Q = 169, $df = 22$, $P < .001$). We repeated the random-effect meta-analysis for each type of parent diagnosis with similar estimates in offspring of parents with schizophrenia, bipolar disorder or depression (table 1).

We next asked how much is the risk of developing SMI increased in offspring of parents with SMI relative to control offspring of healthy parents. The overall random-effect meta-analysis estimated that offspring of parents

**Table 1.** Rates of Mental Disorders in Offspring of Parents With Schizophrenia, Bipolar Disorder, or Depression

| Parent Diagnosis | Offspring Disorder | All Ages | | | | Under 20 Years of Age | | | | Age 20 and Over | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Offspring | | 95% CI | | Offspring | | 95% CI | | Offspring | | 95% CI | |
| | | *n* | Rate | Lower | Upper | *n* | Rate | Lower | Upper | *n* | Rate | Lower | Upper |
| SMI (any) | SMI | 3863 | **0.24** | 0.19 | 0.29 | 2302 | **0.18** | 0.14 | 0.24 | 1561 | **0.32** | 0.24 | 0.42 |
| | Other SMI | 2759 | **0.14** | 0.10 | 0.18 | 1375 | **0.11** | 0.08 | 0.16 | 1384 | **0.16** | 0.11 | 0.23 |
| | Schizophrenia | 1678 | **0.08** | 0.05 | 0.11 | 379 | **0.07** | 0.03 | 0.17 | 1299 | **0.08** | 0.05 | 0.13 |
| | Bipolar | 2449 | **0.05** | 0.03 | 0.06 | 1346 | **0.03** | 0.02 | 0.05 | 1103 | **0.07** | 0.05 | 0.10 |
| | Depression | 3560 | **0.18** | 0.13 | 0.23 | 2050 | **0.16** | 0.11 | 0.23 | 1510 | **0.21** | 0.13 | 0.30 |
| | Anxiety | 3112 | **0.24** | 0.19 | 0.30 | 1993 | **0.27** | 0.21 | 0.34 | 1119 | **0.20** | 0.12 | 0.31 |
| | Disruptive | 2476 | **0.16** | 0.11 | 0.23 | 2135 | **0.18** | 0.12 | 0.25 | 341 | **0.09** | 0.06 | 0.13 |
| | Substance use | 2549 | **0.15** | 0.10 | 0.20 | 1357 | **0.10** | 0.06 | 0.17 | 1192 | **0.21** | 0.15 | 0.27 |
| | ADHD | 2356 | **0.12** | 0.09 | 0.16 | 2020 | **0.13** | 0.10 | 0.18 | 336 | **0.07** | 0.04 | 0.11 |
| | Any disorder | 3302 | **0.55** | 0.50 | 0.61 | 1999 | **0.57** | 0.50 | 0.63 | 1303 | **0.53** | 0.42 | 0.63 |
| Schizophrenia | SMI | 874 | **0.23** | 0.15 | 0.34 | 152 | **0.17** | 0.09 | 0.28 | 722 | **0.27** | 0.16 | 0.41 |
| | Other SMI | 740 | **0.15** | 0.09 | 0.25 | 69 | **0.10** | 0.05 | 0.20 | 671 | **0.16** | 0.09 | 0.29 |
| | Schizophrenia | 816 | **0.12** | 0.08 | 0.18 | 94 | **0.10** | 0.01 | 0.57 | 722 | **0.12** | 0.07 | 0.18 |
| | Bipolar | 481 | **0.03** | 0.02 | 0.05 | 69 | **0.03** | 0.01 | 0.11 | 412 | **0.03** | 0.01 | 0.06 |
| | Depression | 740 | **0.13** | 0.07 | 0.22 | 69 | **0.07** | 0.03 | 0.16 | 671 | **0.14** | 0.08 | 0.26 |
| | Anxiety | 511 | **0.15** | 0.07 | 0.29 | 99 | **0.31** | 0.14 | 0.54 | 412 | **0.08** | 0.05 | 0.14 |
| | Disruptive | 69 | **0.29** | 0.20 | 0.41 | 69 | **0.29** | 0.20 | 0.41 | 0 | | | |
| | Substance use | 528 | **0.20** | 0.11 | 0.34 | 28 | **0.21** | 0.10 | 0.40 | 500 | **0.20** | 0.10 | 0.36 |
| | ADHD | 69 | **0.10** | 0.05 | 0.20 | 69 | **0.10** | 0.05 | 0.20 | 0 | | | |
| | Any disorder | 729 | **0.47** | 0.34 | 0.60 | 58 | **0.52** | 0.35 | 0.68 | 671 | **0.45** | 0.30 | 0.61 |
| Bipolar | SMI | 1492 | **0.20** | 0.15 | 0.26 | 935 | **0.17** | 0.12 | 0.23 | 557 | **0.27** | 0.18 | 0.39 |
| | Other SMI | 1466 | **0.16** | 0.12 | 0.21 | 909 | **0.14** | 0.10 | 0.20 | 557 | **0.19** | 0.10 | 0.31 |
| | Schizophrenia | 581 | **0.04** | 0.02 | 0.10 | 175 | **0.03** | 0.02 | 0.07 | 406 | **0.05** | 0.01 | 0.16 |
| | Bipolar | 1415 | **0.06** | 0.04 | 0.09 | 880 | **0.04** | 0.03 | 0.06 | 535 | **0.10** | 0.07 | 0.12 |
| | Depression | 1466 | **0.14** | 0.11 | 0.18 | 909 | **0.14** | 0.10 | 0.19 | 557 | **0.15** | 0.10 | 0.23 |
| | Anxiety | 1288 | **0.27** | 0.22 | 0.33 | 863 | **0.30** | 0.23 | 0.38 | 425 | **0.21** | 0.18 | 0.25 |
| | Disruptive | 1027 | **0.14** | 0.10 | 0.19 | 898 | **0.15** | 0.12 | 0.20 | 129 | **0.07** | 0.04 | 0.13 |
| | Substance use | 1137 | **0.15** | 0.09 | 0.24 | 712 | **0.12** | 0.05 | 0.26 | 425 | **0.20** | 0.11 | 0.33 |
| | ADHD | 1234 | **0.14** | 0.09 | 0.21 | 898 | **0.17** | 0.11 | 0.25 | 336 | **0.07** | 0.04 | 0.11 |
| | Any disorder | 1285 | **0.60** | 0.53 | 0.67 | 935 | **0.60** | 0.54 | 0.66 | 350 | **0.58** | 0.34 | 0.78 |
| Depression | SMI | 1482 | **0.27** | 0.16 | 0.41 | 1215 | **0.22** | 0.13 | 0.34 | 267 | **0.48** | 0.18 | 0.79 |
| | Other SMI | 553 | **0.06** | 0.02 | 0.16 | 397 | **0.03** | 0.00 | 0.27 | 156 | **0.09** | 0.02 | 0.31 |
| | Schizophrenia | 266 | **0.04** | 0.01 | 0.11 | 110 | **0.08** | 0.04 | 0.15 | 156 | **0.02** | 0.01 | 0.06 |
| | Bipolar | 553 | **0.03** | 0.01 | 0.13 | 397 | **0.01** | 0.01 | 0.03 | 156 | **0.06** | 0.01 | 0.35 |
| | Depression | 1339 | **0.26** | 0.15 | 0.41 | 1072 | **0.22** | 0.11 | 0.39 | 267 | **0.40** | 0.19 | 0.65 |
| | Anxiety | 1298 | **0.29** | 0.19 | 0.43 | 1031 | **0.25** | 0.15 | 0.38 | 267 | **0.43** | 0.23 | 0.67 |
| | Disruptive | 1380 | **0.16** | 0.08 | 0.30 | 1168 | **0.18** | 0.08 | 0.35 | 212 | **0.10** | 0.06 | 0.17 |
| | Substance use | 884 | **0.11** | 0.06 | 0.20 | 617 | **0.07** | 0.03 | 0.13 | 267 | **0.23** | 0.16 | 0.32 |
| | ADHD | 1053 | **0.11** | 0.08 | 0.15 | 1053 | **0.11** | 0.08 | 0.15 | 0 | | | |
| | Any disorder | 1273 | **0.57** | 0.46 | 0.67 | 1006 | **0.53** | 0.42 | 0.64 | 267 | **0.65** | 0.45 | 0.81 |

*Note*: ADHD, attention deficit hyperactivity disorder; SMI, severe mental illness (psychotic or major mood disorder); Other SMI, SMI different from the diagnosis in parent. All rates are absolute rates (ie, a rate of 0.32 means 32% of all high-risk offspring) based on random-effect meta-analyses. Absolute rate estimate is printed in bold, followed by the lower and upper bounds of the 95% CI; *n* is the number of high-risk offspring on whom the estimate is based.

with SMI had a 2.5-fold increased risk of developing SMI compared with matched control offspring (RR = 2.52, 95% CI 2.08–3.06, $P < .001$; figure 2).

### *Specific Mental Disorders in Offspring of Parents With SMI*

We investigated rates of individual disorders and groups of disorders in offspring of parents with each diagnosis (schizophrenia and nonaffective psychoses, bipolar disorder, depression). Results of random-effect meta-analyses are shown in table 1. Overall, 55% of high-risk offspring suffered from any diagnosed mental disorder, with little differences by parental diagnoses. The data for some combinations of parental and offspring disorders were sparse. This was mainly due to most offspring of parents with schizophrenia being studied in adulthood (with little or no data on childhood disorders like ADHD) and most

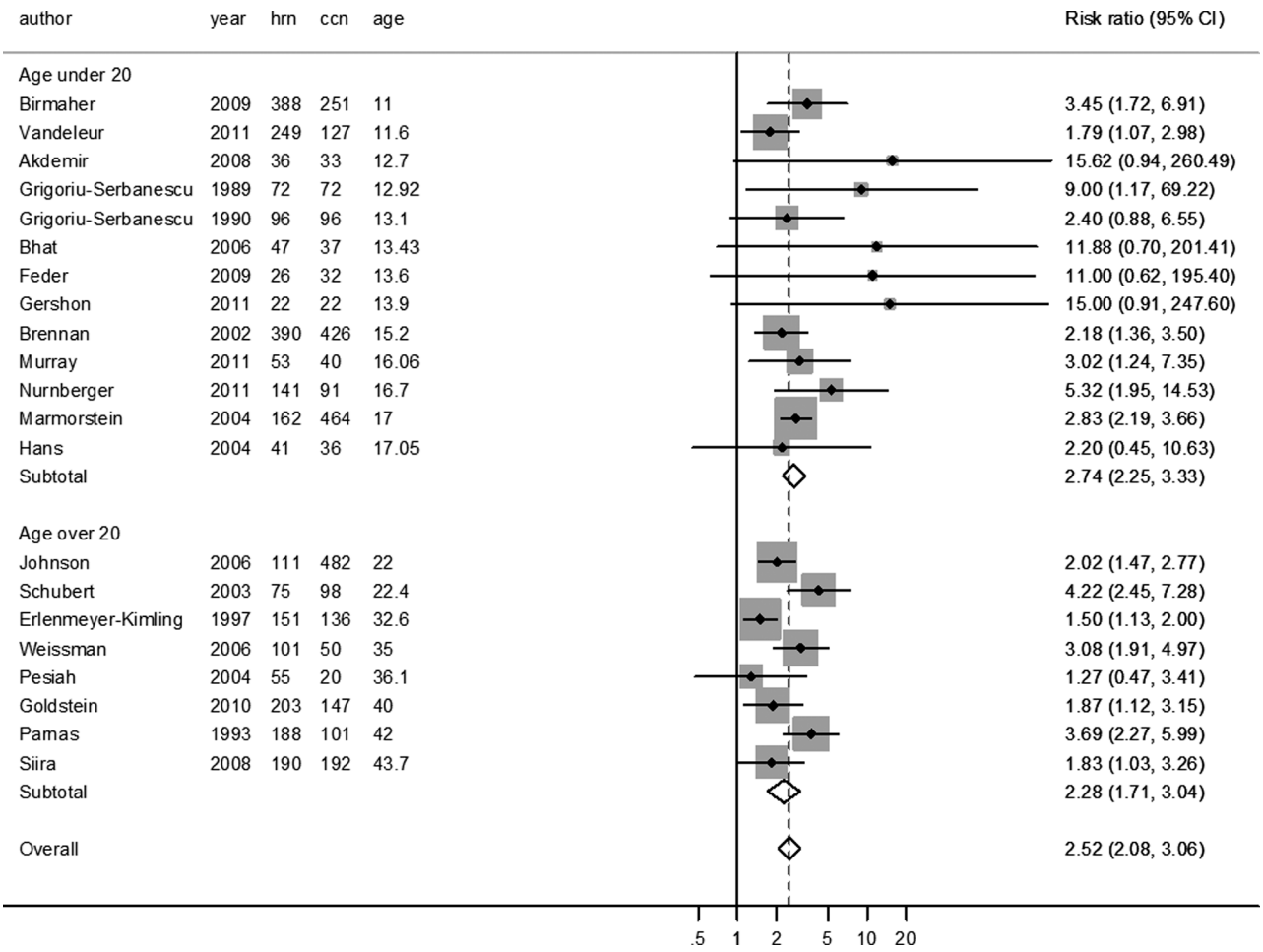


**Fig. 2.** Risk ratio (RR) of severe mental illness (SMI; schizophrenia, bipolar disorder, or depression) in offspring of parents with SMI compared with control offspring of parents with no SMI. Results of random-effect meta-analysis are presented as RR with 95% CI, stratified by mean offspring age at last diagnostic assessment and overall. hrn, number of high-risk offspring; ccn, number of control offspring. For each comparison, the small black diamond symbol in the middle represents the RR of high-risk offspring compared with controls. The horizontal line is the 95% CI. The empty diamonds represent the overall weighted RR for (1) studies of offspring with mean age under of 20 (top), (2) studies of offspring with mean age 20 or older (middle), and (3) overall weighted RR across all studies. The width of the empty diamonds represents their 95% CI.

offspring of parents with depression being studied in adolescence (with little data on disorders with later onset, such as schizophrenia).

### *Specificity of Familial Transmission*

We investigated the RR of developing mental disorders in offspring of parents with schizophrenia, bipolar disorder and depression compared with matched control offspring, overall and stratified by age (table 2). Mental disorders were consistently elevated in offspring of parents with any diagnosis compared with control offspring. There was evidence for partial specificity with largest RR for schizophrenia among offspring of parents with schizophrenia and largest RR for bipolar disorder among offspring of parents with bipolar disorder. There was also evidence of general familial risk: almost all RR were nominally larger than one (the exception were anxiety disorders among offspring of parents with schizophrenia) and 34 of the 66 risk ratios were statistically significant. Robust heterotypical associations included a doubling of the risk of anxiety disorders and increased risk of substance use disorders among adolescent offspring of parents with bipolar disorder and depression (table 2).

We next tested the specificity of familial transmission as a risk of other SMI (other than the disorder diagnosed in the parent), relative to matched control offspring. If familial transmission is disorder specific, these heterotypic risks should not be significantly elevated. However, the random meta-analysis showed that the risk of developing a psychotic or major mood disorder other than the disorder present in parent was increased 1.92 times (95% CI 1.48–2.49, $P < .001$) among offspring of parents with SMI. For comparison, the risk of the same disorder as diagnosed in the parent was increased 3.59-fold (95% CI 2.57–5.02; $P < .001$).

We further examined the risk of other SMI separately for offspring of parents in each diagnostic group. Offspring of parents with schizophrenia had a significantly increased risk of bipolar disorder or major depressive disorder (RR = 1.62, 95% CI 1.02–2.58, $P$ = .042) and offspring of parents with bipolar disorder had a significantly increased risk of schizophrenia or major depressive disorder (RR = 2.03, 95% CI 1.49–2.78, $P$ < .001). Offspring of parents with depression had 4-fold increased risk of developing schizophrenia or bipolar disorder, but due to small numbers of offspring old enough to be at risk for these disorders, this result did not reach statistical significance (RR = 4.07, 95% CI 0.55–30.1, $P$ = .169). The tests of heterotypic transmission of risks between specific types of SMI were underpowered: all RR were nominally larger than 1, but many were not statistically significant (table 2).

## Discussion

When a mother or father with SMI, such as bipolar disorder, asks a clinician how likely it is that their child

**Table 2.** Relative Rates of Mental Disorders in Offspring of Parents With Schizophrenia, Bipolar Disorder, or Depression Compared With Control Offspring of Parents With No SMI

| Parent Diagnosis | Offspring Disorder | All Ages | | | | Under 20 Years of Age | | | | Age 20 and Over | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | RR | Lower | Upper | $P$ | RR | Lower | Upper | $P$ | RR | Lower | Upper | $P$ |
| SMI | SMI | **2.52** | 2.08 | 3.06 | .000 | **2.74** | 2.25 | 3.34 | .000 | **2.28** | 1.71 | 3.05 | .000 |
| | Other SMI | **1.92** | 1.48 | 2.49 | .000 | **2.43** | 1.71 | 3.46 | .000 | **1.67** | 1.21 | 2.29 | .002 |
| | Schizophrenia | **3.94** | 2.03 | 7.63 | .000 | **1.09** | 0.48 | 2.51 | .833 | **6.19** | 3.50 | 10.96 | .000 |
| | Bipolar | **4.04** | 2.33 | 7.01 | .000 | **5.63** | 1.82 | 17.38 | .003 | **3.84** | 1.89 | 7.80 | .000 |
| | Depression | **2.03** | 1.57 | 2.61 | .000 | **2.74** | 2.26 | 3.33 | .000 | **1.52** | 1.06 | 2.17 | .022 |
| | Anxiety | **1.72** | 1.47 | 2.01 | .000 | **1.84** | 1.54 | 2.21 | .000 | **1.47** | 1.11 | 1.96 | .007 |
| | Disruptive | **1.91** | 1.41 | 2.60 | .000 | **1.87** | 1.37 | 2.55 | .000 | **3.22** | 0.76 | 13.71 | .114 |
| | Substance use | **1.56** | 1.28 | 1.90 | .000 | **2.02** | 1.30 | 3.12 | .002 | **1.52** | 1.14 | 2.02 | .005 |
| | ADHD | **1.86** | 1.48 | 2.32 | .000 | **1.86** | 1.48 | 2.32 | .000 | | | | |
| | Any disorder | **1.60** | 1.46 | 1.76 | .000 | **1.77** | 1.61 | 1.96 | .000 | **1.45** | 1.28 | 1.64 | .000 |
| Schizophrenia | SMI | **2.21** | 1.55 | 3.14 | .000 | **2.20** | 0.45 | 10.63 | .329 | **2.21** | 1.51 | 3.25 | .000 |
| | Other SMI | **1.62** | 1.02 | 2.58 | .042 | **1.80** | 0.35 | 9.25 | .481 | **1.61** | 0.97 | 2.67 | .068 |
| | Schizophrenia | **7.54** | 4.02 | 14.13 | .000 | **2.64** | 0.11 | 62.92 | .548 | **7.87** | 4.14 | 14.94 | .000 |
| | Bipolar | **1.84** | 0.73 | 4.66 | .197 | **2.64** | 0.11 | 62.92 | .548 | **1.78** | 0.67 | 4.70 | .244 |
| | Depression | **1.31** | 0.78 | 2.20 | .312 | **1.32** | 0.23 | 7.45 | .755 | **1.31** | 0.74 | 2.31 | .357 |
| | Anxiety | **0.97** | 0.68 | 1.39 | .874 | **1.00** | 0.57 | 1.76 | .990 | **0.95** | 0.60 | 1.50 | .830 |
| | Disruptive | **1.90** | 0.81 | 4.49 | .142 | **1.90** | 0.81 | 4.49 | .142 | | | | |
| | Substance use | **1.72** | 0.88 | 3.37 | .112 | **0.29** | 0.01 | 6.99 | .449 | **1.86** | 0.93 | 3.71 | .079 |
| | ADHD | **1.76** | 0.34 | 9.03 | .500 | **1.76** | 0.34 | 9.03 | .500 | | | | |
| | Any disorder | **1.45** | 1.17 | 1.79 | .001 | | | | | **1.45** | 1.17 | 1.79 | .001 |
| Bipolar | SMI | **2.42** | 1.65 | 3.54 | .000 | **3.46** | 1.97 | 6.09 | .000 | **1.70** | 1.30 | 2.23 | .000 |
| | Other SMI | **2.03** | 1.49 | 2.78 | .000 | **2.81** | 1.73 | 4.58 | .000 | **1.59** | 1.17 | 2.15 | .003 |
| | Schizophrenia | **2.76** | 0.67 | 11.27 | .158 | **0.77** | 0.27 | 2.21 | .622 | **6.42** | 2.20 | 18.78 | .001 |
| | Bipolar | **4.06** | 1.91 | 8.62 | .000 | **6.42** | 1.91 | 21.56 | .003 | **4.13** | 0.66 | 25.91 | .130 |
| | Depression | **2.07** | 1.27 | 3.35 | .003 | **3.20** | 2.05 | 5.00 | .000 | **1.13** | 0.79 | 1.63 | .501 |
| | Anxiety | **1.92** | 1.56 | 2.36 | .000 | **2.01** | 1.59 | 2.52 | .000 | **1.59** | 0.98 | 2.56 | .058 |
| | Disruptive | **1.84** | 1.24 | 2.72 | .002 | **1.84** | 1.24 | 2.72 | .002 | | | | |
| | Substance use | **1.45** | 1.07 | 1.97 | .016 | **1.82** | 1.10 | 3.04 | .021 | **1.28** | 0.88 | 1.87 | .201 |
| | ADHD | **1.62** | 1.23 | 2.13 | .001 | **1.62** | 1.23 | 2.13 | .001 | | | | |
| | Any disorder | **1.66** | 1.50 | 1.83 | .000 | **1.75** | 1.54 | 2.00 | .000 | **1.54** | 1.33 | 1.79 | .000 |
| Depression | SMI | **2.45** | 2.03 | 2.95 | .000 | **2.61** | 2.12 | 3.22 | .000 | **2.21** | 1.50 | 3.26 | .000 |
| | Other SMI | **4.07** | 0.55 | 30.10 | .169 | **1.87** | 0.76 | 4.65 | .176 | **8.49** | 0.43 | 166.86 | .159 |
| | Schizophrenia | **1.52** | 0.63 | 3.64 | .349 | **1.48** | 0.57 | 3.85 | .417 | **1.71** | 0.19 | 15.16 | .631 |
| | Bipolar | **5.03** | 0.90 | 28.18 | .066 | **5.77** | 0.28 | 118.82 | .256 | **4.45** | 0.31 | 63.73 | .272 |
| | Depression | **2.38** | 1.94 | 2.91 | .000 | **2.66** | 2.10 | 3.36 | .000 | **2.05** | 1.57 | 2.68 | .000 |
| | Anxiety | **1.78** | 1.41 | 2.25 | .000 | **2.00** | 1.58 | 2.52 | .000 | **1.41** | 0.79 | 2.54 | .249 |
| | Disruptive | **1.80** | 1.56 | 2.09 | .000 | **1.82** | 1.56 | 2.12 | .000 | **1.63** | 0.69 | 3.87 | .264 |
| | Substance use | **1.72** | 1.30 | 2.27 | .000 | **3.15** | 1.59 | 6.26 | .001 | **1.53** | 1.13 | 2.07 | .006 |
| | ADHD | **2.40** | 1.66 | 3.47 | .000 | **2.40** | 1.66 | 3.47 | .000 | | | | |
| | Any disorder | **1.64** | 1.40 | 1.92 | .000 | **1.82** | 1.57 | 2.10 | .000 | **1.35** | 0.98 | 1.84 | .063 |

*Note*: Abbreviations are explained in the first footnote to table 1. All relative risks, expressed as risk ratios (RR), are based on random-effect meta-analyses. Relative rate estimate, expressed as RR is printed in bold, followed by the lower and upper bounds of the 95% CI and the $P$ value for the rate difference between high-risk and comparison offspring.

will also become ill, the likely answer informed by previous literature is that the risk is about 1 in 10. The present meta-analysis suggests that, by early adulthood, the offspring has a 1-in-3 risk of developing a psychotic or major mood disorder and 1-in-2 risk of developing any mental disorder. Given the limited number of studies on adult offspring of parents with mood disorders and child offspring of parents with schizophrenia, these results should still be considered preliminary. The fact that not all disorders were assessed in most studies and that rates of diagnoses increased with repeated assessments suggest that these may be underestimates. Clinicians should seriously consider how to inform patients of the elevated risks of mental disorders in their children, as the perceived risk can be a factor in decisions of whether or not to have children.[7] Evidence suggests that providing risk descriptors along with probabilities as part of an in-depth discussion with patients reduces the risk of miscommunication and misperception of risk.[5] Following the present results, a clinician may consider the risk of the same disorder, risk of other SMI and risk of less severe mental disorders, taking into account the age of the offspring and the nonnegligible base rates of mental disorders in the general population. Such fine-grained discussion will give the parents and prospective parents honest and complete information.

The specificity of familial transmission of risk is relevant to thinking on etiology of illness, classification of diseases and to the planning of early interventions. The present meta-analysis finds that familial risk extends across diagnostic boundaries. This confirms results from population registry and genetic studies that report overlap of familial and genetic risk to various mental disorders.[2,3,25] The results of the meta-analysis also suggest that familial transmission can be heterotypic (different from parent diagnosis), yet diagnosis specific: the risk of anxiety disorders was elevated in offspring of parents with bipolar disorder or depression, but not in offspring of parents with schizophrenia. The heterotypic familial transmission supports recent findings from molecular genetic analyses suggesting shared genetic factors underlying schizophrenia, bipolar disorder and major depression.[11–13] However, to what extent the observed parent-offspring association is due to genetic factors vs environmental factors remains open.

The finding of limited specificity suggests that cross-disorder approaches may be useful not only in etiological studies but also in planning of early preventive interventions aiming to reduce the risk of SMI. To appreciate the degree of specificity, it is necessary to consider both absolute and relative rates. Because major depressive disorder is more common than schizophrenia, a smaller RR for depression among adult offspring of parents with SMI (RR = 1.52) caused greater increase in the absolute risk of SMI than a higher RR for schizophrenia among adult offspring of parents with SMI (RR = 6.19). When comparing RR and absolute risks, it is clear that homotypic risks are numerically greater (especially in relative terms), but heterotypic risks are still significantly elevated and substantially contribute to the elevated absolute risk for any SMI in offspring of parents with SMI. The fact that familial risk extends across disorders suggests that it may be more efficient to target common mechanisms and antecedents preceding the development of various mood and psychotic disorders.[26,27] Finally, the heterotopy and limited specificity of familial transmission is relevant to the development of psychiatric classification where increasing number of categories contrasts with the lack of evidence supporting most diagnostic boundaries.[28,29] Future research into biological and environmental causes of SMI may be more fruitful if it is not constrained by current consensus diagnostic categories.[30] Future studies may also examine the value of dimensional constructs cutting across the diagnostic categories in explaining heterotypic transmission.

The meta-analysis overcame to some extent the limited statistical power of individual FHR studies to detect smaller cross-diagnostic risks. Yet, the results must be interpreted in the context of limitations inherent in the methodology and heterogeneity of the contributing studies. First, the coverage of offspring of different age was uneven with sparse data for adult disorders among offspring of parents with depression and of childhood disorders among offspring of parents with schizophrenia. This means that some disorder-specific questions (eg, whether the risk of schizophrenia is significantly elevated among offspring of parents with depression) remain open. Some apparently surprising disorder-specific findings may be due to small numbers included. For example, the rate of schizophrenia and related disorders among offspring of parents with schizophrenia aged under 20 was surprisingly high at 10%. However, this estimate was based on a small number of offspring and may not be reliable. This highlights the need for examining more adolescent offspring of parents with schizophrenia. In addition, some cases of major depressive disorders among offspring may be reclassified as bipolar disorder if manic or hypomanic episode develop on further follow-up. Future FHR research would complement current data with investigation of childhood disorders in offspring of parents with schizophrenia and follow-up into adulthood of offspring of parents with mood disorders. Second, the diagnosis of the co-parent was not reported in most studies and as a result we were unable to assess effects of multiple affected parents. These effects may be nonnegligible in context of assortative mating[31,32] and dose-response relationships between the number of affected parents and risk of mental disorders in offspring.[2] Third, most studies made their diagnoses based on single cross-sectional assessment. Cross-sectional assessment has been shown to underestimate the lifetime rates compared with sequential assessments.[33–35] We found that the rates of SMI were higher in longitudinal studies where offspring

were assessed repeatedly. In addition, most offspring had not been followed up through the age of peak risk of SMI onset. Thus, the current results are likely to underestimate the actual lifetime risks.

This meta-analysis of family high-risk studies of SMI found that familial transmission of risk is only partly diagnosis specific. As a result, the total risk of SMI and any mental illness in offspring of parents with psychotic or major mood disorders are higher than previously thought. This should be reflected in genetic counseling and information provided by clinicians. Cross-diagnostic research may be needed to advance the knowledge of etiology and plan effective preventive interventions.

## Supplementary Material

Supplementary material (references 36–67 are cited in the supplementary material) is available at http://schizophreniabulletin.oxfordjournals.org.

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