Mortality in Offspring of Parents With Psychotic Disorders: A Critical Review and Meta-Analysis

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Objective: Mortality risk in offspring of parents with psychotic disorders is a sensitive and important topic, but evidence on which to base plans for preventive services is limited. The authors synthesized evidence for mortality risk among offspring of parents with psychotic disorders and examined potential modifiers of risk such as offspring age and parental diagnosis.

Method: Electronic reference and citation databases were searched. Secondary analyses were carried out to generate relative risk estimates and perform post hoc statistical power calculations. A meta-analysis of the association between maternal psychotic disorder and fetal death/stillbirth was conducted.

Results: Most of the relevant studies investigated the relationship between exposure to maternal schizophrenia and perinatal or infant mortality outcomes but were not truly population-based and lacked adequate power. Studies published since 1960 generally indicated higher than expected mortality risk in exposed offspring. Meta-analysis indicated an almost twofold higher risk of fetal death/stillbirth among offspring of women with psychoses. Notable gaps in the existing evidence include outcome beyond the first year of life, cause-specific mortality, and effects of exposure to specific parental conditions other than schizophrenia and of exposure to paternal versus maternal disorder. Etiological mechanisms are not fully understood.

Conclusions: Large-scale population-based studies are needed to understand mortality risk in offspring of parents with psychoses. In the absence of etiological evidence, only general preventive measures can be taken. Prevention of offspring mortality at an early age is most likely to be achieved by identification and treatment of maternal disorder and greater provision of support to these vulnerable families.

Psychotic disorders affect childbearing in a number of ways, including lower rates of fertility in affected adults (1–3) and higher rates of obstetric complications in affected women (4, 5). Greater risk of fetal, perinatal, and infant mortality among exposed offspring has also been found, although there remains a need for the accurate and precise quantification of risk in the overall population of exposed offspring and in specific high-risk subgroups. In addition to estimation of relative risks for all-cause mortality, the elucidation of cause-specific risks and etiological mechanisms is also required to inform the development of preventive measures and interventions. For example, recent commentary highlighted the need for further research on possible links between parental mental disorder and sudden infant death syndrome (6). Our aim was to synthesize existing published evidence of associations between parental psychotic disorder and all-cause and cause-specific offspring mortality risk among all exposed offspring and according to possible modifiers of risk such as offspring age and sex, parental diagnosis, having the presence of psychotic disorder in both parents, separation from birth parent(s), and socioeconomic status.

Method

Search Strategy

Three electronic databases were searched (MEDLINE for data published from 1966 to the present, EMBASE from 1980, and PsycINFO from 1887) to identify relevant empirical quantitative studies. A broad range of subject headings was used to identify the relevant disorders and diagnoses. For each database search, three main search components (parental psychotic illness, offspring status, mortality) were created by combining subject headings with the "OR" operator, and the three components were then combined together by using the "AND" operator. Relevance was determined by screening titles and abstracts. Reference lists of relevant articles were screened for further potentially relevant studies, and citation searches were conducted by using the ISI Web of Science. The results are reported for the following exposure groups: 1) offspring of parents with schizophrenia and related disorders and 2) offspring of mothers with unspecified psychotic disorders.

Statistical Analyses

For studies where relative risk estimates were not presented, the reported data were used to calculate these estimates, together with their 95% confidence intervals (CIs). This step was not possible if numerators and denominators were not given in full. Relative risks and 95% CIs calculated by the lead author of this review are denoted as relative risk* and 95% CI*, respectively. Where numerators

TABLE 1. Studies Investigating the Association Between Exposure to Parental Psychotic Illness and Offspring Mortality

Study	Year	Study Area	Number of Exposed Offspring	Number of Deaths	Mortality Outcome	Parental Disorders
Essen-Moller (10)	1935	Munich	—[a]	—[a]	—[a]	Parental schizophrenia
Kallmann (11)	1938	Berlin	1,964	—[a]	Death from infancy to age 59 years	Parental schizophrenia
Sobel (12)	1961	New York State	222	18	Stillbirth and neonatal death	Maternal schizophrenia
Paffenbarger et al. (22)	1961	Cincinnati	126	10	Fetal death and neonatal death	Maternal psychosis during pregnancy or postpartum period
Erlenmeyer-Kimling (13)	1968	New York State	1,718	109	Death from infancy to age 15 years	Parental schizophrenia
Lindelius (14)	1970	Southern Sweden	336	141	Death at all ages (from birth onward)	Parental schizophrenia
Rieder et al. (15)	1975	Boston	210[b]	11[c]	Fetal death and neonatal death	Parental schizophrenia spectrum disorders
Modrzewska (16)	1980	Northern Sweden	553	44	Stillbirth and infant death	Parental schizophrenia
Wrede et al. (17)	1984	Helsinki	171	8	Stillbirth and neonatal death	Maternal schizophrenia
Miller and Finnerty (18)	1996	Chicago	36	2	Stillbirth	Maternal schizophrenia and schizoaffective disorder
Bennedsen et al. (20)	2001	Denmark (whole population)	2,230	50	Stillbirth, neonatal death, and postneonatal death	Maternal schizophrenia
Nilsson et al. (21)	2002	Sweden (whole population)	2,096	40	Stillbirth and infant death	Maternal schizophrenia
Howard et al. (23)	2003	United Kingdom	986	10	Stillbirth and infant death	Maternal psychotic disorders
Jablensky et al. (19)	2005	Western Australia (whole population)	3,174[d]	59[e]	Stillbirth, neonatal death, postneonatal death, and childhood death	Maternal schizophrenia and affective disorders (bipolar disorder and unipolar depression)

[a] Not known.
[b] Includes offspring with exposure to parental schizophrenia (N=93), possible schizophrenia/schizophrenic spectrum (N=60), and other disorders (N=57).
[c] Includes deaths among offspring with exposure to schizophrenia (N=7), possible schizophrenia/schizophrenic spectrum (N=2), and other disorders (N=2).

and denominators were fully reported, post hoc power calculations were performed to enable assessment of the degree of statistical power available to detect relative risks of two- to fourfold.

Meta-analyses were planned to examine mortality in the following offspring age categories: fetal, neonatal (birth to 28 completed days), postneonatal (29th day to end of first year), preschool age (1–4 years), school age (5–15 years), and young adults (16–30 years). However, because of the lack of relevant studies, the formal meta-analysis was performed only for the association between exposure to maternal psychotic disorder and fetal death/stillbirth.

Summary of Findings for Exposed Offspring	Key Strengths of Study	Key Weaknesses of Study
No evidence of a difference in risk of mortality for offspring with exposure to parental schizophrenia per se or by schizophrenia subtype	None	Original report not available in English
Threefold higher risk of suicide, no evidence for a higher risk of all-cause mortality	Highly detailed original account	Difficult to identify key results due to evolution of reporting formats and standards
Twofold higher risk of perinatal death, threefold higher risk of congenital malformation	Adequately powered population-based study	Difficult to appraise due to evolution of reporting formats and standards
Twofold higher risk of fetal or neonatal death	Women sampled as a case series of all first-onset episodes in a city area	Difficult to appraise due to evolution of reporting formats and standards, low statistical power
Lower infant mortality rate (30% lower in males and 60% lower in females), lower mortality rate in females ages 0–15 years (30% lower)	Well-powered population-based study, relatively long offspring follow-up period	Difficult to appraise due to evolution of reporting formats and standards, alternative explanations and reasons for differences in outcome by offspring sex not explored, impossible to compare effects of exposure to paternal versus maternal disorder
Lower mortality rate (approximately 50% lower) at ages 0–4 years, slightly lower mortality rate for all other age groups up to and including ≥50 years	Long offspring follow-up period	Difficult to appraise due to evolution of reporting formats and standards, impossible to compare effects of exposure to paternal versus maternal disorder, probable bias due to low comparability of reference population
Suggestion of higher risk of fetal or neonatal death in offspring of parents with schizophrenia (estimate was nonsignificant and imprecise), no evidence for higher risk in other groups of exposed offspring	Data sampled from a large population-based perinatal survey	Underpowered to investigate offspring mortality outcomes by specific maternal diagnoses, impossible to compare effects of exposure to paternal versus maternal disorder
Threefold higher risk of stillbirth, fourfold higher risk of infant death	Data sampled from a demographically stable isolated rural area	Inadequate statistical power, impossible to compare effects of exposure to paternal versus maternal disorder, unusual study location (low generalizability)
Suggestion of higher risk of stillbirth and perinatal death (estimates were nonsignificant and imprecise, only one death in the comparison group)	Population-based study with sampling from a psychiatric register, medical records used to check diagnostic accuracy	Very low statistical power, possible low follow-up rate for offspring exposed to chronic maternal illness
No evidence of a difference in risk of stillbirth (insufficient sample size)	None	Very small sample size, very low statistical power, study design and sampling procedures not clearly described, missing data regarding history of stillbirth, implausibly high stillbirth rates
One-and-a-half-fold higher risk of stillbirth, threefold higher risk of postneonatal death, fivefold higher risk of sudden infant death syndrome, twofold higher risk of congenital malformation	Large truly population-based national study that enabled investigation of cause-specific mortality (i.e., sudden infant death syndrome)	Potential problem of reverse causality in classification of exposure status, inability to adjust for socioeconomic status
Twofold higher risk of stillbirth and infant death, some evidence for additional excess risk if the mother was first admitted during pregnancy	Large truly population-based national study that enabled investigation of three different definitions of exposure to maternal disorder, with adjustment for socioeconomic status	Inadequate power to investigate effects of exposure to maternal disorder with onset during pregnancy
Fourfold higher risk of stillbirth (significantly higher risk of neonatal and infant death, but relative risk not estimable)	Population-based study with research database of primary care records	Inadequate statistical power, effects of specific maternal diagnoses not explored
No evidence of higher risk of stillbirth, neonatal death, or postneonatal death (suggestion of higher mortality risk during early childhood associated with maternal schizophrenia [imprecise estimate])	Large truly population-based study, follow-up beyond infancy, first published study to investigate specific effect of exposure to maternal bipolar disorder	Underpowered to investigate mortality outcomes by offspring age and by specific maternal diagnoses

[d] Includes offspring with exposure to parental schizophrenia (N=618), bipolar disorder (N=1,301), and unipolar depression (N=1,255).
[e] Numbers of deaths were estimated on the basis of percentages presented in the original paper (Table 5 in reference 19). Total includes deaths among offspring with exposure to schizophrenia (N=15), bipolar disorder (N=26), and unipolar depression (N=18).

Psychotic disorder was defined broadly as schizophrenia and related disorders or any other psychotic disorder. Mantel-Haenszel pooled risk ratios were estimated, with a chi-square test for heterogeneity used to assess between-study differences in effect (7). Fixed-effects models were fitted if there was no evidence of heterogeneity (p<0.1), and risk ratios are presented as a forest plot (8). The forest plot shows study-specific risk ratios (and their 95% CIs) and the relative weighted contribution of each study, as well as the risk ratio estimate pooled across all studies. The analyses were performed with Stata statistical software (9).

Results

Summary of Relevant Studies

Sixteen relevant empirical quantitative studies of mortality in offspring of parents with psychotic disorders published between 1935 and 2004 were identified (10–25), all but two (10, 11) of which were published since 1960. Most studies investigated the effect of parental schizophrenia per se (10, 11, 13–16) or the specific effect of maternal schizophrenia (12, 17–21). Jablensky et al. (19) also investigated maternal affective disorders (unipolar depression and bipolar disorder) as separate exposure categories. The other studies investigated the effects of unspecified postpartum psychosis (22, 23) and a range of maternal disorders, including psychotic illnesses (24, 25). Most studies investigated fetal, perinatal, or infant mortality outcomes, although some of the earlier studies included longer follow-up periods, such as 0 to 59 years (11), 0 to 15 years (13), and 0 to ≥50 years (14). Thus, there was a lack of recent evidence for mortality risk in exposed offspring beyond the first year of life. The quality of the evidence was varied, with the more recent population-based studies conducted with national registries being of the highest quality (19–21). One original report was not translated into English (10), and one study (18) was excluded from the meta-analysis because of poor quality (specifically, small sample size and missing data). One study (24) was excluded from the critical review because of an insufficient number of mothers with psychotic disorders, and another (25) was excluded because results for psychotic disorders were not reported separately from results for nonpsychotic disorders. The 14 studies included in the critical review are summarized in Table 1.

Outcomes for Offspring of Parents With Schizophrenia and Related Disorders

The earliest studies were conducted in Germany (10, 11). The account of the first published study, by Essen-Moller, is available only in German (10), although Kallmann (11) briefly summarized Essen-Moller's findings in English. In Essen-Moller's study, probands were admitted with schizophrenia in Munich during 1904–1927, but the offspring sample size and follow-up period were not reported. No differences in mortality risk were found between exposed offspring overall and the general population, and there was no evidence for heterogeneity of effect by clinical form of schizophrenia, by maternal versus paternal disorder, or by timing of schizophrenia onset.

In Kallmann's study (11), outcomes for offspring (N=2,120) of schizophrenic probands admitted in Berlin during 1892–1902 were investigated. His findings, similar to those of Essen-Moller, were that child mortality risk was independent of schizophrenia per se, of the specific form of the disease, and of the sex of the affected parent. However, the risks of mortality because of suicide and tuberculosis were higher than expected, with four- to fivefold

higher proportional mortality rates for those causes. The proportion of all offspring who died by suicide was also reported (relative risk*=3.3, 95% CI* not estimable).

Rosenthal (26) postulated a "double dose" effect of inherited mortality risk in offspring of two schizophrenic parents. Testing this hypothesis in a secondary analysis of Kallmann's data, he found no evidence of greater risk; 35% of these offspring (N=55) died before age 5 years, compared to 44.5% of the offspring with one affected parent. He also postulated that several gestational conditions could generate additional risk of poor outcome specific to maternal (versus paternal) schizophrenia. These conditions included medication toxicity, coma-inducing or convulsive therapy, inadequate diet, unusually high anxiety or excitatory states, and failure to exercise because of catatonia. He compared mortality to age 5 years in offspring of affected mothers (43.5%) versus fathers (39%) and again found insufficient evidence from Kallmann's data to support this second hypothesis.

Sobel (12) examined data for offspring (N=222) of women with schizophrenia who delivered at New York State mental hospitals during 1950–1958. He reported a perinatal mortality rate of 8.1% (10 stillbirths, eight neonatal deaths), compared with 3.6% in the U.S. general population (relative risk*=2.3, 95% CI* not estimable); the rate of congenital malformations was 3.2% (seven cases), compared with approximately 1% in the national population (relative risk*= 3.2, 95% CI* not estimable). Sobel argued that the incidence of "deviant fetal growth" and subsequent mortality risk could be higher among offspring of mothers with some subtypes of schizophrenia, thereby highlighting the need for using large data sets for investigation of these rare outcomes. Sobel's study was the first published study to empirically indicate higher than expected risk of all-cause mortality among exposed offspring.

However, in accordance with the "physiological advantage hypothesis" of Huxley et al. (27), Erlenmeyer-Kimling (13) postulated that offspring of people with schizophrenia would have *lower* mortality risk. This hypothesis suggests the existence of genetic compensatory advantages that overcome selective disadvantages such as lower fertility and fecundity and render offspring of affected parents fitter than the general population. Examples of possible advantages given by Huxley et al. include "extreme resistance" to surgical or wound shock, burns, pain, arthritis, and many allergies and infections. To test the hypothesis, Erlenmeyer-Kimling calculated mortality rates in offspring (N=1,718) born during 1900–1959 to schizophrenic probands admitted to psychiatric hospitals in New York State and compared these rates with national population rates. The risk of infant mortality (i.e., deaths of live-born offspring during the first year of life) was lower among exposed offspring, a difference that was greater in girls (relative risk=0.4*, 95% CI* not estimable) than in boys (relative risk*=0.7). Relative risks were below 1.0 for both sexes in the 1–4-year age group, although this apparent protective

effect was weak. For offspring ages 5–15 years, the relative risks were greater than 1.0 (relative risk*=1.3 in girls; relative risk*=1.2 in boys). When the data were pooled across all ages (0–15 years), there was no evidence of an effect for boys (relative risk*=1.0), but mortality risk was significantly lower among exposed girls (relative risk*=0.7). These results provided some support for the physiological advantage hypothesis, although no account was taken of possible environmental factors that could explain the lower risks found among exposed infants and young children. For example, institutionalization may have led to a lower prevalence of environmental hazards. Furthermore, no explanation for the heterogeneity of effect by offspring sex was offered.

Lindelius (14) investigated mortality in offspring (N=336) of schizophrenic probands admitted during 1900–1910 in a demographically stable area of rural Sweden, with 93% follow-up to 1960 achieved by using parish registers. Expected numbers of deaths per age-sex stratum were estimated in reference to national population rates and were compared with observed numbers. All-cause mortality was significantly lower than expected in exposed offspring to age 4 years, but, as the author suggested, this finding may have been a statistical artifact that occurred because the national reference rates included higher-risk urban populations. For all other age-sex strata, up to and through adulthood, all-cause mortality was slightly lower than expected in the exposed offspring. There was some indication of a higher mortality rate because of tuberculosis and a lower risk of suicide, although these cause-specific analyses lacked statistical power.

Using data from a large perinatal survey established in 1959 in Boston, Rieder et al. (15) investigated fetal and neonatal mortality in three parental diagnostic subgroups: 1) schizophrenia (N=93), 2) possible schizophrenia/schizophrenic spectrum (N=60), and 3) other disorders (neuroses, manic depression, "character disorder," alcohol addiction with psychosis) (N=57). Comparison subjects without a psychiatric history were selected and matched with the psychiatric disorder subjects for ethnicity, socioeconomic status, maternal age, parity, and offspring multiplicity. There was some suggestion of a higher than expected risk for exposure group 1 only (relative risk*=2.0, 95% CI*=0.7–5.5), although the wide confidence interval indicates imprecision and nonsignificance.

Modrzewska (16) examined data for offspring of parents with schizophrenia (N=553) and comparison subjects with unaffected parents (N=624) in an isolated area of northern Sweden. All probands were born in the area during 1829–1960. Higher than expected risks of stillbirth (relative risk*=3.1, 95% CI*=1.3–7.2) and infant mortality (relative risk*=4.1, 95% CI*=1.8–9.5) were observed in exposed offspring. Low numbers precluded assessment of mortality risk in offspring with two affected parents (N=39), and cause of death could not be investigated because of poor documentation. Furthermore, a high prevalence of con-

sanguineous marriage and intensive inbreeding affected the study's external validity.

Wrede et al. (17) used a psychiatric register to investigate outcomes for offspring born to women with schizophrenia in Helsinki, Finland, during 1960–1964. Medical records were examined to assess diagnostic accuracy, and exposure status in terms of severity of maternal disorder was classified as "chronic" (permanent social deficit: N=54) or "mild" (1–3 admissions: N=117). Comparison subjects were randomly sampled from a population register (N=171). Nine perinatal deaths occurred, all but one among the mild exposure group (four stillbirths, four neonatal deaths) and the other among the comparison subjects (a stillbirth). The lack of deaths in the chronic exposure group was unexpected but could have occurred by chance or because of the high rate of loss to follow-up in that group. For all exposed offspring combined (N=171), the relative risks of stillbirth (relative risk*=4.0, 95% CI*=0.5–35.4) and perinatal mortality (relative risk*=8.0, 95% CI*=1.0–63.3) were higher than expected, but the confidence intervals for these estimates are very wide and imprecise.

Miller and Finnerty (18) recruited women meeting the Research Diagnostic Criteria for schizophrenia or schizoaffective disorder (N=44) in Chicago during 1993–1995 and a comparison group (N=50) of women without major mental illness who were matched with the schizophrenic subjects for age, ethnicity, and socioeconomic status. Subjects were questioned about their sexuality, pregnancies, and child rearing, but there were missing data concerning history of stillbirth (data on history of stillbirth were available for 36 affected women and 46 comparison subjects). Comparable stillbirth rates were reported in the two groups (two cases in the affected group, three in the comparison group), but this evidence is weak because of the small sample sizes and because the baseline risk of stillbirth reported in the comparison group (65 per 1,000) was approximately nine times higher than the contemporary national rate (28).

Jablensky et al. (19, 29) linked population and psychiatric registers to investigate mortality among all births occurring in Western Australia during 1980–1992 to mothers with schizophrenia (N=618), bipolar disorder (N=1,301), and unipolar depression (N=1,255). Comparison offspring (N=3,129) of mothers without a psychiatric history were randomly selected from the general population. There was no evidence of higher than expected perinatal or infant mortality among offspring exposed to maternal schizophrenia (stillbirth: odds ratio=0.8, 95% CI=0.3–2.3; neonatal death: odds ratio=1.0, 95% CI=0.3–3.0; postneonatal death: odds ratio=1.1, 95% CI=0.2–5.1). There was a suggestion that these offspring were at increased risk during early childhood (odds ratio=2.2, 95% CI=0.7–7.3), although this estimate lacked statistical significance and precision. No evidence was found for higher risk of mortality at any age among offspring exposed to maternal bipolar disorder (stillbirth: odds ratio=

TABLE 2. Statistical Power to Detect a Two- to Fourfold Relative Risk for All-Cause Mortality in Studies Investigating the Association Between Exposure to Parental Psychotic Illness and Offspring Mortality

Study	Year	Parental Disorder	Mortality Outcome	Number of Exposed Offspring	Number of Unexposed Offspring	Mortality Risk in Unexposed Offspring (%)	Statistical Power to Detect Relative Risk (%)		
							Twofold Relative Risk	Threefold Relative Risk	Fourfold Relative Risk
Sobel (12)	1961	Maternal schizophrenia	Stillbirth and neonatal death	222	≈36.2 million[a]	3.6	70	99	100
Paffenbarger et al. (22)	1961	Maternal psychosis (during pregnancy or postpartum period)	Fetal death and neonatal death	126	252	2.4	18	31	57
Erlenmeyer-Kimling (13)	1968	Parental schizophrenia	Infant death (females)	817	≈92.3 million[a]	5.8	100	100	100
			Infant death (males)	892	≈88.7 million[a]	7.2	100	100	100
Rieder et al. (15)	1975	Parental schizophrenia	Fetal death and neonatal death	93	186	3.8	21	58	84
		Parental schizophrenia and possible schizophrenia/ schizophrenic spectrum	Fetal death and neonatal death	153	306	3.6	33	78	96
Modrzewska (16)	1980	Parental schizophrenia	Stillbirth	553	624	1.1	25	67	91
			Infant death	534	617	1.1	24	66	90
Wrede et al. (17)	1984	Maternal schizophrenia	Stillbirth and neonatal death	171	171	0.6	3	8	15
Miller and Finnerty (18)	1996	Maternal schizophrenia and schizoaffective disorder	Stillbirth	36	46	6.5	10	31	57
Bennedsen et al. (20)	2001	Maternal schizophrenia	Stillbirth	2,230	123,544	0.5	80	100	100
			Neonatal death	2,212	122,932	0.5	81	100	100
			Postneonatal death	2,196	122,294	0.3	55	93	99
			Sudden infant death syndrome	2,196	122,294	0.1	27	64	85
			Malformations	746	56,106	1.2	73	99	100
Nilsson et al. (21)	2002	Maternal schizophrenia (at any time)	Stillbirth	2,096	1,555,975	0.3	64	97	100
			Infant death	2,081	1,550,656	0.5	78	99	100
		Maternal schizophrenia (before birth)	Stillbirth	935	1,555,975	0.3	37	78	94
			Infant death	927	1,550,656	0.5	48	89	98
		Maternal schizophrenia (during pregnancy)	Stillbirth	201	1,555,975	0.3	11	30	48
			Infant death	198	1,550,656	0.5	15	39	60
Howard et al. (23)	2003	Maternal psychotic disorders	Stillbirth	199	787	0.6	10	29	49
Jablensky et al. (19)	2005	Maternal schizophrenia	Stillbirth	618	3,129	0.8	41	83	97
			Neonatal death	614	3,104	0.6	32	73	92
			Postneonatal death	610	3,086	0.4	22	56	80
			Childhood death	607	3,073	0.3	17	45	69

[a] The authors of the original studies used U.S. general population data to estimate the number of unexposed offspring (data for 1950–1958 were used by Sobel; data for 1900–1959 were used by Erlenmeyer-Kimling). The numbers of live births in the U.S. general population were not reported for either study. In this meta-analysis, the denominators were estimated by the first author with data from the National Center for Health Statistics from 1909 onward (http://www.cdc.gov/nchs/data/statab/t991x01.pdf) (accessed March 31, 2005).

0.9, 95% CI=0.4–1.9; neonatal death: odds ratio=0.8, 95% CI=0.3–2.0; postneonatal death: odds ratio=1.2, 95% CI=0.5–3.0; early childhood death: odds ratio=1.3, 95% CI=0.4–4.6). However, as Table 2 shows, these data lacked power for examining offspring mortality in relation to specific maternal disorders, as the primary aim of the study was to investigate more commonly occurring outcomes during pregnancy, delivery, and the neonatal period.

Two large Scandinavian registry-based studies (20, 21) have provided the best available evidence to date. Bennedsen et al. (20) investigated all single births (N=2,230) to mothers admitted with schizophrenia to public psychiatric facilities in Denmark during 1969–1993; the comparison group consisted of subjects randomly sampled from the general population (N=123,544). As there were no private psychiatric inpatient facilities in Denmark, this investigation was truly a population-based

study. Relative risks were adjusted for year of birth, offspring sex, maternal age, and parity, although no adjustment was made for socioeconomic status, smoking status, substance abuse, and psychoactive treatment. Higher than expected relative risks in exposed offspring were observed for stillbirth (relative risk=1.6, 95% CI=1.0–2.6; adjusted relative risk=1.5, 95% CI=0.9–2.4), neonatal death (relative risk=1.4, 95% CI=0.9–2.3; adjusted relative risk=1.3, 95% CI=0.8–2.1), and congenital malformation (relative risk=1.8, 95% CI=1.1–2.9; adjusted relative risk=1.7, 95% CI=1.0–2.8), with larger effects observed for postneonatal death (relative risk=2.8, 95% CI=1.7–4.5; adjusted relative risk=2.8, 95% CI=1.7–4.6) and sudden infant death syndrome (relative risk=4.7, 95% CI=2.6–8.8; adjusted relative risk=5.2, 95% CI=2.8–9.7). However, offspring were classified as being "exposed" even if the first maternal admission for schizophrenia occurred after the offspring death, an event that could be a contributory factor in maternal disease onset, thereby introducing a potential reverse causation bias (30).

Nilsson et al. (21) conducted a similar investigation of all single births during 1983–1997 to mothers admitted with schizophrenia in Sweden during 1977–1997. Comparison subjects were offspring of unaffected mothers in the general population (N=1.56 million). Potential problems of reverse causality were addressed by estimating relative risks for three exposed subgroups: 1) offspring of mothers who first received the diagnosis at any time during the study period (N=2,096), 2) offspring of mothers who first received the diagnosis before birth of the offspring (N=935), and 3) offspring of mothers who first received the diagnosis during pregnancy (N=201), with groups 2 and 3 providing the more stringent definitions of exposure. Odds ratios were estimated with adjustment for maternal age, smoking, education, country of birth, marital status, and the presence of pregnancy-induced hypertension. Offspring whose mothers received the diagnosis of schizophrenia before the offspring's birth were found to be at higher than expected risk for stillbirth (odds ratio=2.5, 95% CI=1.3–5.1; adjusted odds ratio=1.7, 95% CI=0.9–3.5), and they also had a higher—although nonsignificantly higher—risk for infant death (odds ratio=1.8, 95% CI=0.9–3.6; adjusted odds ratio=1.4, 95% CI=0.7–2.8). There was some indication of even greater risk if the mother's first admission occurred during pregnancy (stillbirth: odds ratio=4.4, 95% CI=1.4–13.8; adjusted odds ratio=2.5, 95% CI=0.8–7.9) (infant death: odds ratio=3.1, 95% CI=1.0–9.8; adjusted odds ratio=2.1, 95% CI=0.7–6.6), although these subgroup analyses lack statistical precision.

Outcomes for Offspring of Mothers With Unspecified Psychotic Disorders

Paffenbarger et al. (22) used inpatient records to identify women ages 15–44 years (N=126) with first-onset psychotic episodes during pregnancy (or in the 6 months prior to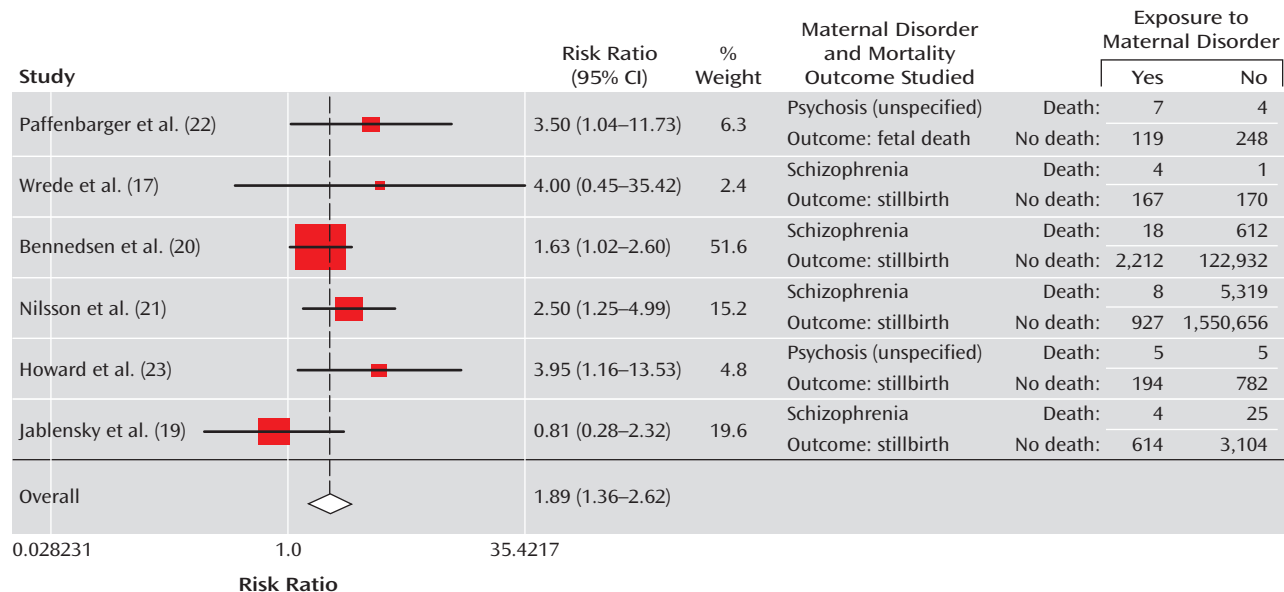 pregnancy) in 1940–1958 in Cincinnati. Obstetric data were obtained, and comparison subjects (N=252), matched for maternity unit and ethnicity, were also selected. There were 10 deaths among exposed offspring (seven fetal deaths and three neonatal deaths) and six among the comparison subjects (four fetal deaths and two neonatal deaths). The fetal and neonatal death rates, adjusted for maternal age and parity, were twice as high in exposed offspring than in the comparison offspring (7% versus 3%) (p=0.02).

Howard et al. (23) conducted a population-based retrospective cohort study in England using the General Practice Research Database. Outcomes in offspring born during 1996–1998 to women with a diagnosis of a psychotic disorder (N=199) were compared to those of offspring born to comparison subjects (N=787) matched for maternal age and general practice. Five stillbirths occurred in both groups—a significantly greater proportion among the exposed group (2.5% versus 0.6%) (odds ratio=4.0, 95% CI=1.1–4.3). Four neonatal deaths and one postneonatal death also occurred among exposed offspring, compared with none among the live-born comparison subjects.

Two other studies were conducted to investigate the effects of a broad range of maternal psychiatric illnesses, including psychotic disorders. Zax et al. (24) analyzed data for offspring of women with schizophrenia (N=29), neurotic depression (N=56), and personality disorder (N=42) in Rochester, N.Y., from 1959 onward. Bagedahl-Strindlund et al. (25) investigated outcome for offspring born to women (N=177) with a diagnosis of unspecified functional psychoses (19%), schizophrenia and schizoaffective disorder (16%), affective disorder (28%), neuroses (23%), and alcohol/drug addiction (14%) in Stockholm County, Sweden, during 1976–1977. In both investigations, mothers with psychotic illnesses constituted a minority of the sample. The study by Zax et al. included too few women with psychotic disorders, and Bagedahl-Strindlund et al. did not report results separately for women with psychotic versus nonpsychotic disorders. For these reasons, the results of these two studies were excluded from the review.

Meta-Analysis

A meta-analysis of the relationship between maternal psychotic disorder and fetal death/stillbirth was performed, as there were a sufficient number of relevant studies that met the criteria for meta-analysis (N=6) (17, 19–23). Studies were excluded from the meta-analysis for the following reasons: 1) stillbirth rates were not reported (10, 11, 13, 14), 2) results were not reported separately for psychotic versus nonpsychotic disorders (24, 25), 3) paternal disorder was also included in the "exposed" offspring category (15, 16), or 4) numerators or denominators for the reference population were not reported (12). Another study (18) was excluded because of poor quality. All six studies included in the meta-analysis were published since 1960, and all but one (22) were published from the

FIGURE 1. Meta-Analysis of Exposure to Maternal Psychotic Disorder and Fetal Death/Stillbirth Rate[a]

Study	Risk Ratio (95% CI)	% Weight	Maternal Disorder and Mortality Outcome Studied		Exposure to Maternal Disorder Yes	No
Paffenbarger et al. (22)	3.50 (1.04–11.73)	6.3	Psychosis (unspecified)	Death:	7	4
			Outcome: fetal death	No death:	119	248
Wrede et al. (17)	4.00 (0.45–35.42)	2.4	Schizophrenia	Death:	4	1
			Outcome: stillbirth	No death:	167	170
Bennedsen et al. (20)	1.63 (1.02–2.60)	51.6	Schizophrenia	Death:	18	612
			Outcome: stillbirth	No death:	2,212	122,932
Nilsson et al. (21)	2.50 (1.25–4.99)	15.2	Schizophrenia	Death:	8	5,319
			Outcome: stillbirth	No death:	927	1,550,656
Howard et al. (23)	3.95 (1.16–13.53)	4.8	Psychosis (unspecified)	Death:	5	5
			Outcome: stillbirth	No death:	194	782
Jablensky et al. (19)	0.81 (0.28–2.32)	19.6	Schizophrenia	Death:	4	25
			Outcome: stillbirth	No death:	614	3,104
Overall	1.89 (1.36–2.62)					

0.028231   1.0   35.4217

Risk Ratio

[a] Test for heterogeneity: $\chi^2=6.35$, df=5, p=0.27 (the nonsignificant p value indicates no evidence for variation in the study-specific risk ratios. The fixed-effects model presented here thus provides a reasonable summary of the results from the studies in the meta-analysis).

mid-1980s onward, which probably reflects the evolution of accepted methods of scientific reporting.

The results are presented in Figure 1. The pooled estimate indicated a doubling of mortality risk in exposed offspring (Mantel-Haenszel pooled relative risk*=1.9, 95% CI*=1.4–2.6). In all but one study—Jablensky et al. (19)—the relative risk was above 1.0, and there was no evidence of between-study heterogeneity ($\chi^2=6.35$, df=5, p=0.27). Exclusion of studies is unlikely to have materially altered the results, as almost all studies published since 1960 indicated a higher than expected risk of fetal death/stillbirth.

Discussion

Summary of Main Findings

On the basis of informal interpretation and formal meta-analysis, the evidence published since 1960 generally indicated that exposure to maternal psychotic illness is associated with a higher than expected risk of perinatal and infant mortality. Meta-analysis indicated an almost twofold relative risk for fetal death/stillbirth among offspring of affected mothers, which is comparable in magnitude to that observed for maternal smoking during pregnancy (31). Between 1968 and 1980, four studies were published that included offspring exposed to paternal schizophrenia (13–16). In each of these studies, the relative risk for exposure to parental versus maternal disorder was not estimable because the data were not reported separately, and statistical power for making such a comparison was in any case lacking. Our findings indicate a need for evidence concerning the effects of exposure to paternal disorder. Other important gaps in the evidence base

are highlighted and discussed in the later section on "Lessons for Future Research."

Putative Causal Mechanisms

Existing evidence suggests that causal mechanisms vary according to offspring age. Thus a combination of genetic, antenatal, and obstetric factors may explain the higher risks of fetal, perinatal, and neonatal death in exposed offspring; for example, an as yet unspecified common genetic or environmental mechanism linking schizophrenia and congenital malformation has been suggested (20). Women with schizophrenia are more likely to continue smoking or misusing substances during pregnancy and to have unrecognized comorbid medical conditions (32). Women with schizophrenia and other mental disorders also tend to have lower attendance at or poorer quality antenatal care visits (33–36). These factors, together with low socioeconomic status (37), may explain the higher likelihood of restricted fetal growth and preterm birth observed in offspring of women with schizophrenia, which in turn strongly predicts increased risk of perinatal and infant mortality (38).

Psychotropic medication toxicity may also cause congenital malformation and fetal, perinatal, and neonatal death, but existing evidence in this area is inconclusive (37, 39). It could be that these potentially adverse effects are a recent phenomenon, as most early studies failed to show a higher risk of mortality (10, 11, 13, 14), and dopamine-receptor-blocking drug treatment for schizophrenia was not introduced until the 1950s. Indeed Sobel's 1961 study (12) was the first to indicate higher mortality risks. Evidence for a greater incidence of obstetric complications is also equivocal (37). Using Danish national regis-

ters, Bennedsen et al. (36) found that offspring of mothers with schizophrenia tended to have lower Apgar scores, but there was no evidence of a greater incidence for specific complications. In an Australian register-based study, Jablensky et al. (19) reported higher rates of pregnancy, obstetric, and neonatal complications, such as placental abnormality, antepartum hemorrhage, and fetal distress, in women with schizophrenia and affective disorder. Two meta-analyses have also indicated higher risk of complication during pregnancy and birth in women with schizophrenia (4, 5).

During infancy and childhood, offspring of mentally ill people may be more likely to experience neglect and adverse domestic environments (25, 40). Brown and Davidson (41) investigated accident rates in children (N=420) ages <16 years in inner London and found a strong interaction between social class and maternal psychiatric disorder (p<0.001). The highest accident rate was observed among offspring of affected working-class mothers (19.2 per 100 children per year), followed by offspring of unaffected working-class mothers (9.6 per 100), offspring of affected middle-class mothers (5.3 per 100), and offspring of unaffected middle-class mothers (1.5 per 100).

Salmon et al. (42) investigated the prevalence of parenting problems after joint mother-infant psychiatric admissions in England. Nine percent of all women admitted (N=1,081) and 21% of those with schizophrenia (N=223) were perceived by staff to be at significant risk of harming their infants on discharge, although the study used a broad definition of harm that included emotional abuse and neglect. Using the same data, Howard et al. (43) found that 23% of all women admitted and 48% of those with schizophrenia were discharged under formal social service supervision. Investigation of a large community-based sample of more than 8,000 adults in Ontario, Canada, suggested two- to threefold higher rates of self-reported childhood physical or sexual abuse in offspring of mentally ill people, with especially high risk if either parent had an antisocial disorder (44). However, this evidence is weakened because of a high likelihood of biased recall among adult subjects, which may result in information bias in estimating prevalence of abuse during childhood. Furthermore, severity of abuse and subsequent mortality risk were not explored.

No population-based studies of offspring homicide by parents with psychotic illness were identified in the review. Bennedsen et al. (20) reported a high relative risk for sudden infant death syndrome in the offspring of schizophrenic mothers, which, as the authors pointed out, could include an unknown number of disguised homicides. The possibility of homicide in sudden infant death syndrome is controversial, and estimating the frequency of such events at the population level has to date proved impossible. Also the extreme rarity of these events would suggest that, even if relative risks for this outcome were higher, the phenomenon would explain little of the overall excess mortality risk.

When offspring reach adolescence, higher rates of mental disorder and substance misuse, as well as risk-taking, violent, or suicidal behavior, may place exposed offspring at higher mortality risk. For example, Chang et al. (45) found mental disorder in more than one-half of their sample (ages 6–18 years) of offspring of people with bipolar disorder, and Brent et al. (46) estimated a sixfold higher risk of suicide attempt in the offspring of index attempters. Our review found no population-based studies of mortality during adolescence and early adulthood in offspring of affected parents.

Lessons for Future Research

This review highlighted important gaps in the following areas of the current evidence base:

- The effect of exposure to paternal versus maternal disorder and of exposure to two affected parents versus one affected parent
- The modifying effects of offspring sex and age, specifically risk of mortality beyond the first year of life
- Cause-specific mortality and etiological mechanisms and pathways
- The effect of exposure to disorders other than maternal schizophrenia (e.g., bipolar disorder, dual diagnosis)
- The confounding and modifying effects of factors such as socioeconomic status and separation from birth parent(s)

Two of these points are particularly noteworthy. First, our review identified only one study (19) that specifically investigated mortality risk associated with maternal bipolar disorder, and, as reported in the Results section, there was no evidence of higher risk of mortality in these offspring. In earlier studies these mothers are likely to have been misclassified as having other diagnoses, but to an unknown degree. Benazzi and Akiskal (47) found that about one-half of patients with major depressive episodes have type II bipolar disorder, and Thomas (48) reported that the disorder is often misdiagnosed as schizophrenia in the postpartum period because of the presence of "extreme psychotic and mixed features." Thus, the prevalence of bipolarity may be higher than previously thought (48), and even high-quality registry-based studies tend to exclude patients with less severe forms of the disorder (49). Investigation of the effects of maternal bipolar disorder in an evolving diagnostic framework is a challenge for future research. Second, in all studies reviewed there were no data regarding the frequency or effect of temporary or permanent removal of offspring from their birth parent(s). The prevalence of parent-offspring separation is known to be high in this group (43), and separation could be an important modifier of risk. These infants and children may be at higher risk because of the introduction of an inferior substitute child-rearing environment, or conversely, they could be at lower risk because of the removal of exposure to neglect and other hazards that are directly related to the

parental psychotic disorder. Parent-offspring separation could also be an important source of bias, as these offspring may be more likely to be lost to follow-up. Family setting (i.e., whether the infant is raised in a two-parent family, by a single mother, or in some other type of setting) could also be an important modifier of risk. These factors have not been investigated to date, as the relevant variables do not currently exist in national registers.

Future investigators should also be aware that most of the studies identified in this review had two fundamental methodological flaws: 1) they were not truly population based and 2) they lacked sufficiently large sample sizes to detect main effects with precision and had only minimal statistical power for detecting interactions and conducting subgroup analyses.

Table 2 presents post hoc statistical power calculations. The relevant information was not available for three studies (10, 11, 14). These calculations indicate that, with the exception of four studies (12, 13, 20, 21), investigations published to date have lacked adequate power to detect a twofold relative risk for all-cause mortality as a main effect. Even the large registry-based studies were underpowered to investigate effects in subgroups such as offspring exposed to onset of maternal schizophrenia during pregnancy (21).

Sample sizes have been inadequate because of the rarity of mortality at a young age and because of logistical problems in recruiting and prospectively following up large population-based samples. Because of the general downward trend in perinatal, infant, and childhood mortality rates over the last four decades, even larger sample sizes are now required. Also, some studies have primarily assessed more commonly occurring outcomes, such as disease inheritance (e.g., Modrzewska [16]), pregnancy and obstetric complications (e.g., Jablensky et al. [19]), or health care utilization (e.g., Howard et al. [23]), with mortality outcomes reported as secondary findings. This review strongly indicates a need for the use of comprehensive computerized national registers to investigate offspring mortality at the whole-population level. To detect main and subgroup effects with precision, sample sizes of several thousand offspring within each exposure group of interest are required.

Two register-based Scandinavian studies (20, 21) that were set up specifically to investigate offspring mortality outcomes have provided the best evidence to date. Record linkage between general population and psychiatric admission registers offers the potential for conducting truly population-based longitudinal studies (50–52). These registers are ideal for investigation of this topic, for the following reasons:

1. Statistical modeling of rare events, such as cause-specific mortality in children and young adults, is possible. The registers provide sufficient statistical power to investigate subgroup effects as well as main effects with precision.

2. The biases that are common to many epidemiological surveys are minimal. For example, information bias is low, as data for explanatory and outcome variables are collected prospectively so that equivalent information is obtained irrespective of subsequent outcome status. Loss to follow-up occurs only through migration from the country. Analysis of cause-specific mortality can take into account competing risks, because deaths due to other causes are recorded.

3. High levels of ascertainment for both explanatory and outcome variables are achieved through mandatory participation. Data validity and accuracy are also generally high, and record linkage is achieved with almost total completeness by using a unique personal identifier.

4. A whole population cohort can be studied retrospectively over several decades.

Implications for Service Development

High-quality evidence is required to inform risk management strategies across the various agencies that assess needs and provide care, such as mental health, primary care, maternal and child health, and social service agencies. The future development of these services is dependent on successful identification and elucidation of causal mechanisms that are specific to parental diagnoses and offspring age. In the absence of this evidence, preventive strategies should focus on achieving 1) improved standards of maternity care, including screening and early treatment of psychotic disorder during antenatal and postnatal periods; 2) enhanced multiagency support for affected families with infants and young children; and 3) better parenting skills for people with psychotic illnesses.

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