

Parental schizophrenia and increased offspring suicide risk: exploring the causal hypothesis using cousin comparisons

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Background. Little is known about suicide risk among offspring of parents hospitalized for schizophrenia and the mechanisms behind this association.

Method. We applied a nested case–control design based on linkage of Swedish population-based registers. Among 12- to 30-year-old offspring, we identified 68 318 offspring with suicidal behavior (attempted and completed suicide) and their parents. Five healthy control–parent pairs were matched to each suicidal case–parent pair and conditional logistic regression used to obtain odds ratios (ORs). Further, to disentangle familial confounding from causal environmental mechanisms, we compared the population-based suicide risk with the risk found within full-cousins and half-cousins differentially exposed to parental schizophrenia.

Results. Offspring of parents with schizophrenia had significantly increased suicide risk after accounting for socio-economic status, parental suicidal behavior and offspring mental illness [OR 1.68, 95% confidence interval (CI) 1.53–1.85]. Suicide risks in offspring of schizophrenic mothers and fathers were similar in magnitude; so were risks across different developmental periods. Importantly, offspring suicide risk remained essentially unchanged across genetically different relationships; offspring of siblings discordant for schizophrenia had equivalent risk increases within full-cousins (OR 1.96, 95% CI 1.66–2.31) and half-cousins (OR 1.69, 95% CI 1.17–2.44).

Conclusions. Parental schizophrenia was associated with increased risk of offspring suicidal behavior, independent of gender of the schizophrenic parent, and persisting into adulthood. The suicide risk in offspring remained at a similar level when comparing genetically different relationships, which suggests that at least part of the association is due to environmental mechanisms. These findings should inspire increased attention to suicidal ideation and prevention efforts in offspring of parents with schizophrenia.

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Introduction

Offspring of parents hospitalized for psychiatric disorders are at increased risk of death from unnatural causes (Hiroeh *et al.* 2001; Webb *et al.* 2007; Chen *et al.* 2010). The few studies that have addressed specific psychiatric diagnoses and suicidal behavior indicate increased risk of suicidal behavior among offspring of parents with schizophrenia (Mittendorfer-Rutz *et al.* 2008; Stenager & Qin, 2008). Specifically,

schizophrenia is a major chronic mental disorder that severely afflicts the individual with this disorder and the rearing environment for children over prolonged periods compared with other psychiatric disorders (Henriksson & McNeil, 2004; Abel *et al.* 2005). Thus, very little is known about the mechanisms underlying this association, whether environmental risk factors affect offspring suicide risk or if the association is due to a common genetic susceptibility for schizophrenia and suicidal behavior. Further, it is uncertain if there are different developmental periods where the suicide risk is particularly pronounced, whether the risk of offspring suicidal behavior is independent of the gender of the parent with schizophrenia, and to what extent potential covariates account for the association.

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A better understanding of the mechanisms underlying the association between parental schizophrenia and offspring suicidal behavior is central to help the identification of targets for possible suicide intervention efforts.

Family studies have indicated that genetic factors are important in nearly all mental illnesses (Kendler *et al.* 2003) and also for suicidal behavior (Brent, 2010; Tidemalm *et al.* 2011). In particular, offspring of parents with schizophrenia have higher genetic liability of developing these illnesses themselves (Gottesman & Bertelsen, 1989; Lichtenstein *et al.* 2009). Also, nearly 80% of all individuals with suicidal behavior have a prior or concurrent mental disorder (Nock *et al.* 2010). Consequently, if offspring suicidal behavior and parental schizophrenia are influenced by the same genetic effects, the shared genetic liability would create an increased risk of suicidal behavior among offspring of schizophrenic parents. Besides possible genetic mechanisms, offspring suicide risk could also be increased through mentally ill parents' influence on the family environment (e.g. impaired ability to care for their children) (Gould *et al.* 1996; Johnson *et al.* 2002). Also, individuals diagnosed with schizophrenia more often experience risky environments, such as completed suicide in non-offspring relatives (Palmer *et al.* 2005) and domestic violence (Brennan *et al.* 2000), which has been suggested to increase offspring suicide risk (Johnson *et al.* 2002; Brent & Mann, 2005). Thus, both genetic and environmental mechanisms might influence the association between parental schizophrenia and offspring suicidal behavior.

Suicidal behavior among offspring of schizophrenic parents might be linked to specific developmental periods. Prior findings indicate an increased risk of death due to unnatural causes in preschool children (Webb *et al.* 2007; Chen *et al.* 2010) and suicidal behavior in early adulthood (Webb *et al.* 2007) among offspring of parents with mental illness. However, due to small samples very little is known about suicide risk in adolescence (Webb *et al.* 2005). Previous research has also suggested that the association between parental care-giving and child behavior is stronger for maternal compared with paternal behavior. This is perhaps best explained by mothers traditionally being primary child caregivers and, thus, more involved in their children's daily problems (Rothbaum & Weisz, 1994). Actually, studies have found increased levels of completed suicides in daughters of mothers with schizophrenia (Stenager & Qin, 2008), while others have found a higher suicide risk especially in offspring of schizophrenic fathers (Webb *et al.* 2007), although research on fathers with schizophrenia and their effect on offspring psychosocial development has been limited (Ramchandani & Psychogiou, 2009). Former

research has also been hampered by the fact that other risk factors for offspring suicide, such as socio-economic factors (e.g. low income, unemployment and disability) (Qin *et al.* 2003), have not been adequately adjusted for (Webb *et al.* 2006, 2007). Similarly, the contribution of potentially mediating covariates for the association between parental schizophrenia and offspring suicidal behavior such as a family history of suicidal behavior (Qin *et al.* 2002; Lieb *et al.* 2005) and offspring mental illness (Qin & Nordentoft, 2005) has not been explored in detail. In particular, since suicidal behavior is not only associated with schizophrenia but also with bipolar disorder, depression, substance abuse and personality disorder (Tidemalm *et al.* 2008; Ilgen *et al.* 2010), different psychiatric disorders in offspring might mediate the effect.

We aimed to evaluate the suicide risk among offspring of parents hospitalized for schizophrenia by using a total population sample in Sweden and, if present, to disentangle the mechanism behind this association. Possible mechanisms were addressed using both measured covariates to control for several central predictors of offspring suicidal behavior among parents with schizophrenia and by comparing suicide risks in cousins differentially exposed to parental schizophrenia. We had three secondary objectives: to explore whether suicide risk among offspring of patients with schizophrenia is more pronounced during specific periods of life; to explore if the risk differs by gender of the parent afflicted by schizophrenia; and, finally, to investigate the influence of suggested mediating risk factors underlying the association between parental schizophrenia and offspring suicidal behavior.

Method

Data sources

This study was based on a record linkage with five nationwide, longitudinal registers, with the personal identification number, unique for all residents in Sweden, as key.

The Swedish Multi-Generation Register (MGR, held by Statistics Sweden), links all children (index persons) born in Sweden since 1932 and alive in 1961 to their biological or adoptive parents. This holds also for those who emigrated and became Swedish citizens before 18 years of age. The spouse of the mother is assumed to be the biological father of the index person; the fatherhood is otherwise reported by the mother (Statistics Sweden, 2006). Psychiatric disorders (main diagnoses, secondary diagnoses, and external causes of injury and poisoning from in-patient care) are registered with complete national coverage in

the National Patient Register (National Board of Health and Welfare) from 1973 and onward. The Cause of Death Register (National Board of Health and Welfare) includes all deceased persons registered in Sweden at the time of death with information on the underlying and multiple contributory causes of death. Information on highest attained educational level is recorded in LISA, a longitudinal integration database for health insurance and labor market studies holding annual registers since 1990. Dates of all emigration and immigration are found in the Migration Register (Statistics Sweden).

Subjects

We linked index persons in the Multi-Generation Register to their biological mother and father. The study base was restricted to births before 31 December 1996, to ensure that all offspring were at least 12 years old at the end of 2008, which resulted in almost 14 million unique child–parent relationships.

Selected cases were singleton births, aged 12–30 years, which had either attempted or completed suicide and whose parents were born in Sweden. To reduce possible misclassifications, suicidal behavior in children younger than 12 years was excluded. We also excluded individuals with younger siblings with suicidal behavior to obtain a more homogeneous sample. In all, our study included 68 318 unique suicide cases.

To each suicide case–parent pair we matched five pairs of offspring–parent controls. Eligible as controls were offspring who had not died, emigrated, or expressed suicidal behavior at the year of the case's suicide event. Controls were matched on birth year, gender, and country of birth of the suicide case and on birth year and gender of the parent afflicted by schizophrenia. The study was approved by the Regional Ethics Committee at Karolinska Institutet.

Measures

Outcome: offspring suicide

Suicide attempts were recorded as main or secondary diagnoses from in-patient care in the National Patient Register and defined as certain [International Classification of Diseases (ICD)-8–9: E950–E959, ICD-10: X60–X84] or uncertain suicide attempts (ICD-8–9: E980–E989; ICD-10: Y10–Y34). Completed suicides were defined as definite (ICD-8–9: E950–E959, ICD-10: X60–X84) and uncertain suicides (ICD-8–9: E980–E989, ICD-10: Y10–Y34) in the Cause of Death register. Self-poisoning by solid or liquid substances and injury by hanging or strangulation were the most common methods used among adolescents and young adults

during the study period. Hanging was somewhat more prevalent among completed suicides compared with attempted suicides (7% and 2%, respectively), whereas poisoning was more common among attempted suicides (57% and 69%, respectively).

Exposure: parental schizophrenia

Schizophrenia was defined according to the discharge diagnoses (ICD-8 and ICD-9: 295; ICD-10: F20). This was done hierarchically, that is, we allowed for co-occurring bipolar disorder (ICD-8: 296.1, 296.3, 296.8; ICD-9: 296A, 296C–E, 296W; ICD-10: F30–F31). Offspring were not considered exposed if parents had a late onset of schizophrenia (after 60 years of age). Previous validation studies have indicated low numbers of false-positive diagnoses of schizophrenia in Swedish registers (Ekholm *et al.* 2005).

Covariates

Socio-economic status (SES) was considered a possible confounder for the association between parental schizophrenia and offspring suicidal behavior, and was adjusted for in the analyses. SES was assessed by highest attained education level in the parent, and categorized into three groups: elementary education (9 years or less), secondary education (10–12 years), and any higher education (13 years or more).

The contributions of potential mediators, such as parental suicidal behavior and offspring mental illness, were assessed by adjusting for these factors individually in the analyses. Parental suicidal behavior was defined using the same criteria as for offspring suicidal behavior. We only considered offspring exposed to parental suicidal behavior if it occurred before the offspring suicidal behavior. Offspring mental illness was defined as any in-patient diagnosis of schizophrenia, other non-organic psychotic disorder, bipolar disorder, affective, anxiety, phobic, obsessive, dissociative, somatoform, alcohol/drug use or personality disorder (ICD-8: 291, 295, 296.0–296.3, 296.8–296.9, 297–301, 303, 304; ICD-9: 291–292, 295, 296A–296E, 296W–296X, 297–298, 300–301, 303–304, 305X, 311; and ICD-10: F10–F25, F28–F31, F32.0–F32.3, F32.8–F32.9, F33–F42, F44–F45, F48, F60–F62) assigned before the offspring suicide event and for the control offspring before the suicidal behavior of the matching case.

Statistical analyses

First, we evaluated the suicide risk among offspring of parents with schizophrenia by using a nested case–control design. Second, a cousin comparison

design was used to investigate the influence of genetic and environmental mechanisms on this association.

Nested case-control design

We included cases and controls between 12 and 30 years of age and used conditional logistic regression to calculate odds ratios (ORs) with 95% confidence intervals (CIs). We used a sandwich estimator to supply robust standard errors corrected for the dependence between repeated observations within clusters. Analyses were performed in SAS 9.2 using the PHREG procedure (SAS Institute Inc., USA). We calculated crude ORs for differences between cases and controls matched for birth year, gender, and country of birth of the suicide case and on birth year and gender of the parent. We consecutively adjusted for potential effect of education, parental suicidal behavior and offspring mental illness to examine the distinctive effect from the respective risk factors/mediators. Risks were estimated both separately for attempted and completed suicide and with both outcomes. In the combined analyses, individuals with both attempted and completed suicide were included as a case in the year of the suicide attempt.

In subgroup analyses, we stratified by offspring age at suicide: 12–18 years (adolescents), 19–25 years (young adulthood) and 26–30 years (adulthood). We chose the youngest stratum cut-off at 18 years since practically everyone has accomplished formal education up to this age in Sweden (hence providing covariate data). Young adults were stratified into two parts to explore potential differences during the development. The age of 30 years was chosen as the maximum upper end cut-off point since the effect of exposure to parental schizophrenia is most probably reduced at higher ages. Additionally, the analyses were stratified by gender of the parent suffering from schizophrenia.

Cousin comparison design

To study possible familial confounding we also applied cousin comparison analyses. Again, we used the interlinked population-based registers to identify all parental sibling pairs (both full-siblings and half-siblings) discordant for schizophrenia. To ensure that all offspring were at least 12 years old we only included offspring born before the end of 1996. We excluded twin parents since monozygotic twins are genetically identical and their children (who are cousins) would have the same genetic resemblance as siblings have. Each index parent with schizophrenia was only counted once. Thus, in families with more than two siblings (e.g. if a schizophrenic sibling would

have two healthy siblings) we only included the two discordant siblings with lowest age difference. In total, 4947 unique sibling pairs discordant for schizophrenia and their children were used for cousin comparison analyses.

We explored the importance of familial risk factors (genetic and early environmental) by comparing the risk of suicidal behavior within full-cousins, and half-cousins (whose parents are half-siblings) differentially exposed for a parent with schizophrenia. If the suicide risk within differentially exposed full- and half-cousins remains at the same level as that within the unrelated general population, this indicates an environmental association.

In contrast, if the risk of suicide within differentially exposed full-cousins is diminished compared with the risk in half-cousins, the results would indicate that the association is confounded by genetic mechanisms; because full-cousins share 12.5% of their segregating genes while half-cousins only share 6.25%. Specifically, if parental schizophrenia and offspring suicidal behavior are influenced by the same genetic effects, we would expect offspring of the schizophrenic parent (of a discordant sibling pair) to inherit some susceptibility genes from their parent, resulting in a high risk of suicide. Likewise, if genetic effects are of importance, we would expect a more moderate risk of suicidal behavior in offspring of the healthy parent as these children also inherit some part of the susceptibility genes. Thus, the risk within differentially exposed full-cousins would be markedly attenuated compared with the overall risk in the population. Correspondingly, if genetic effects are important, we expect the suicide risk among half-cousins differentially exposed for parental schizophrenia to be somewhat attenuated compared with the risk obtained with population controls.

Results

Descriptive statistics

We identified 68 318 cases with suicidal behavior (57% male and 43% female) aged 12–30 years, born between 1939 and 1996. Percentages of cases with a suicide attempt and completed suicide were 90.2% and 12.4%, respectively. Thus, 1748 cases had both a suicide attempt and completed suicide. Linking the suicide cases with their known biological mother and father resulted in 123 329 offspring–parent pairs and 594 839 matched offspring–parent pair controls. Among all participants, there were 107 families where both parents had an admission for schizophrenia. Descriptive information is presented in Table 1. A fraction of all cases and controls (3.4%

Table 1. Characteristics of suicidal behavior case–parent pairs and matched control–parent pairs among offspring aged 12–30 years, born and living in Sweden, between 1939 and 1996

	Case pairs	Control pairs
Relationship, <i>n</i>		
Offspring–parent	123 329	594 839
Offspring–mother	63 236	304 891
Offspring–father	60 093	289 948
Highest attained parental education, <i>n</i> (%)		
Elementary education (≤ 9 years)	46 764 (37.9)	213 654 (35.9)
Secondary education (10–12 years)	50 882 (41.2)	243 816 (41.0)
Higher education (≥ 13 years)	21 448 (17.4)	120 829 (20.3)
Missing data	4235 (3.4)	16 540 (2.7)
Any parental suicide	5180 (4.2)	12 227 (2.1)
Any offspring mental illness	20 289 (16.5)	7672 (1.3)

and 2.7%, respectively) lacked information regarding education level and were hence excluded from the models. In general, controls had a somewhat higher education level than cases; 20% of the parents of controls had completed higher education compared with 17% of the parents of cases. The prevalence of suicide was about twice as high in parents of cases compared with parents of controls. Offspring mental illness and suicidal behavior were strongly associated; a history of mental illness was more than 10 times higher among suicidal behavior cases compared with controls.

Risk factors

Crude and adjusted ORs for associations of parental schizophrenia and offspring suicidal behavior are presented in the first row of Table 2. Results from the crude but matched analysis suggested a statistically significant increased risk of suicidal behavior in offspring of parents with schizophrenia (OR 2.28, 95% CI 2.10–2.47). The association remained significant even after adjusting for education alone (OR 2.22, 95% CI 2.05–2.41), and further adjustment for parental suicidal behavior (OR 1.90, 95% CI 1.74–2.07) and offspring mental illness (OR 1.68, 95% CI 1.53–1.85).

Age-stratified results (Table 2) revealed similar risk estimates across the three age groups [with crude ORs ranging between 2.14 and 2.39 (column 3) and adjusted ORs between 1.74 and 1.52 (column 6)], suggesting that the risk associated with parental schizophrenia is only weakly attenuated across different developmental periods up to the age of 30 years. Table 2 also indicated that offspring suicide risk was similarly increased independently of

the gender of the parent that suffered from schizophrenia.

Separate ORs for attempted and completed suicide are presented in Table 3; we found an excess risk of completed suicide among offspring of parents with schizophrenia (OR 2.54, 95% CI 2.03–3.18), but the effect size was not significantly different from that for attempted suicide (OR 2.27, 95% CI 2.09–2.48). Similar to the findings for the combined measure suicidal behavior, risks of completed and attempted suicide did not vary according to tested age strata or gender of the parent diagnosed with schizophrenia (data not shown).

Cousin comparisons

We identified 4285 pairs of full-siblings and 662 pairs of half-siblings discordant for schizophrenia (see Table 4). For each sibling relationship, Table 4 shows the proportion of suicidal behavior in offspring of siblings with and without schizophrenia. The proportion of offspring suicidal behavior in the general population was 4.06% and 1.74% among parents with and without schizophrenia, respectively. The suicide risk was, independent of familial relationship (half- or full-siblings), roughly doubled for offspring of parents with schizophrenia. Specifically, offspring suicide risk compared with unrelated matched population controls (OR 2.28, 95% CI 2.10–2.47) was comparable to the risk observed within differentially exposed full-cousins (OR 1.96, 95% CI 1.66–2.31) and half-cousins (OR 1.69, 95% CI 1.17–2.44). These results suggested that the association between parental schizophrenia and offspring suicidal behavior remained, even after controlling for familial (genetic or shared environmental) confounding. We also

Table 2. Overall and age-specific risk of suicidal behavior in offspring of parents with schizophrenia

	Number of pairs		Odds ratio (95% CI)			
	Cases	Controls	Crude ^a	Adjusted ^b	Adjusted ^c	Adjusted ^d
Parents						
Total	119 092	568 104	2.28 (2.10–2.47)	2.22 (2.05–2.41)	1.90 (1.74–2.07)	1.68 (1.53–1.85)
Adolescents (12–18 years)	35 829	172 436	2.14 (1.84–2.48)	2.07 (1.78–2.40)	1.73 (1.48–2.02)	1.74 (1.49–2.03)
Young adults (19–25 years)	54 621	260 469	2.32 (2.06–2.62)	2.27 (2.01–2.56)	1.94 (1.71–2.20)	1.72 (1.49–1.98)
Adults (26–30 years)	28 642	135 199	2.39 (2.03–2.82)	2.34 (1.99–2.76)	2.06 (1.74–2.43)	1.52 (1.22–1.89)
Mothers						
Total	61 855	295 673	2.25 (2.03–2.50)	2.19 (1.97–2.43)	1.83 (1.64–2.03)	1.63 (1.45–1.84)
Adolescents (12–18 years)	18 317	88 188	1.94 (1.59–2.36)	1.86 (1.53–2.27)	1.47 (1.20–1.81)	1.47 (1.20–1.80)
Young adults (19–25 years)	28 242	135 081	2.39 (2.05–2.78)	2.32 (1.99–2.71)	1.95 (1.66–2.29)	1.78 (1.49–2.13)
Adults (26–30 years)	15 296	72 404	2.40 (1.98–2.91)	2.34 (1.93–2.83)	2.05 (1.68–2.51)	1.59 (1.24–2.03)
Fathers						
Total	57 237	272 431	2.33 (2.04–2.65)	2.29 (2.01–2.61)	2.03 (1.77–2.32)	1.72 (1.46–2.02)
Adolescents (12–18 years)	17 512	84 248	2.46 (1.97–3.08)	2.40 (1.92–3.00)	2.15 (1.70–2.71)	2.17 (1.72–2.74)
Young adults (19–25 years)	26 379	125 388	2.21 (1.82–2.68)	2.18 (1.79–2.65)	1.92 (1.57–2.35)	1.61 (1.26–2.06)
Adults (26–30 years)	13 346	62 795	2.39 (1.78–3.20)	2.35 (1.75–3.17)	2.08 (1.53–2.84)	1.38 (0.89–2.13)

CI, Confidence interval.

^a Crude estimates were obtained by comparing cases and controls matched for gender, birth year and country of birth.

^b Obtained by adjusting for covariates in footnote a and education level.

^c Obtained by adjusting for covariates in footnote a, education level and parental suicide.

^d Obtained by adjusting for covariates in footnote a, education level, parental suicide and offspring mental illness.

Table 3. Overall risk of suicidal behavior in offspring of parents with schizophrenia by attempted and completed suicide

	Number of pairs		Odds ratio (95% CI)	
	Cases	Controls	Crude ^a	Adjusted ^b
Any suicidal behavior	119 092	568 104	2.28 (2.10–2.47)	1.68 (1.53–1.85)
Attempted suicide	108 366	517 336	2.27 (2.09–2.48)	1.67 (1.51–1.84)
Completed suicide	13 521	64 136	2.54 (2.03–3.18)	2.18 (1.68–2.82)

CI, Confidence interval.

^a Crude estimates were obtained by comparing cases and controls matched for gender, birth year and country of birth.

^b Obtained by adjusting for covariates in footnote a and for education level, parental suicide and offspring mental illness.

conducted cousin comparison analyses separately by attempted and completed suicide. Again, the risks within differentially exposed full-cousins (attempted: OR 2.02, 95% CI 1.70–2.40; completed: OR 1.93, 95% CI 1.27–2.95) were not markedly attenuated compared with total population controls. Again, this indicated that the effect of parental schizophrenia on offspring attempted and completed suicide was at least partly driven by environmental mechanisms. Unfortunately, due to the limited number of cases, we had insufficient power to investigate the risk of attempted and completed suicide among discordant half-siblings.

Discussion

This is the first population-based study of the risk of suicidal behavior from early adolescence through young adulthood among offspring of parents with schizophrenia. We observed a robust two-fold risk increase across different periods of life for this association, which is in line with prior research investigating the association between parental schizophrenia and unnatural causes of death (Webb *et al.* 2007; Stenager & Qin, 2008). We also found a doubled suicide risk in offspring regardless of whether the mother or the

Table 4. Absolute and relative risks of suicidal behavior among cousins differentially exposed for parental schizophrenia

Parental relationship	Pairs	Exposed		Unexposed		Odds ratio (95% CI)
		No. of offspring suicides	Proportion, %	No. of offspring suicides	Proportion, %	
Full-cousins	4285	385	4.81	242	2.51	1.96 (1.66–2.31)
Half-cousins	662	71	5.77	51	3.50	1.69 (1.17–2.44)

CI, Confidence interval.

father had schizophrenia. Risks remained similar when tested separately for attempted and completed suicide (and not only for the composite suicidal behavior measure). Further, and importantly, the suicide risk was of similar magnitude when comparing cousins differentially exposed for parental schizophrenia. Thus, our results suggest that the association between parental schizophrenia and offspring suicidal behavior is due at least partly to environmental mechanisms.

Although earlier findings strongly suggest that suicidal behavior runs in families (Brent, 2010; Tidemalm *et al.* 2011), the mechanisms underlying the association between severe parental mental illness and suicidal behavior in offspring have not been clarified. We found that the risk of suicide within cousins differentially exposed for parental schizophrenia remained at a similar level regardless of parental sibling relatedness (i.e. full *v.* half-siblings), which indicates that environmental factors play an important role in the association between parental schizophrenia and offspring suicidal behavior. In line with our findings, several earlier studies have indicated that environmental factors such as the quality of the parent–child relationship (Gould *et al.* 1996), lack of parental communication or support (Gould *et al.* 1996), and maladaptive parenting and child abuse (Johnson *et al.* 2002) are important risk factors for suicidal behavior in offspring. Such parental and parenting characteristics might increase offspring introverted behavior, avoidance of social contacts, hopelessness and suicidal behavior (Bridge *et al.* 2006). Although few studies have investigated the strength of the association between specific psychiatric diagnoses and suicidal behavior (Ilgen *et al.* 2010), prior research indicates that individuals with schizophrenia have elevated suicide risk themselves (Ilgen *et al.* 2010). Hence, in addition to the various core symptoms of schizophrenia *per se*, suicidal ideation might also affect the ability to interact with and care for one's children, which is likely to contribute to offspring suicide risk. In addition, a recent study reported

higher offspring suicide risk the more recently a parent had been admitted for mental illness (Stenager & Qin, 2008), supporting that offspring suicidal behavior is likely to be influenced by parental mental illness through emotional and environmental effects, rather than via a shared genetic basis only. In line with this, a recent Finnish adoption study showed that mortality among adoptees with high risk of schizophrenia was not related to genetic background but rather environmental factors, such as an unhealthy life-style (Hakko *et al.* 2011). Conversely, results from family and adoption studies indicate that familial transmission of suicidal behavior in some part is attributable to genetic factors (Schulsinger *et al.* 1979; Tidemalm *et al.* 2011; Von Borczyskowski *et al.* 2011). Thus, although our results indicate that environmental mechanisms play an important role in the association between parental schizophrenia and offspring suicidal behavior, we could not entirely rule out genetic influences.

In accordance with prior findings (Nock *et al.* 2008), we observed higher rates of attempted suicides during adolescents and young adults, and also that such behaviors were more prevalent among women while completed suicides were more common among men. This is possibly explained by males' use of more lethal methods (such as hanging) compared with the majority of females' use of self-poisoning methods (Beautrais, 2004). There was, however, no evidence of an excess risk of completed suicide compared with attempted suicide among offspring of parents diagnosed with schizophrenia. We observed a two-fold increased risk of both attempted and completed suicide independent of different periods of life and of the gender of the schizophrenic parent. These finding indicates that the risk associated with parental schizophrenia acts across a spectrum of suicidal behaviors.

Previous research with Swedish register data suggested that offspring exposed to parental suicide in childhood or adolescence had the highest risk of committing suicide themselves (Wilcox *et al.* 2010). In contrast, we found that offspring suicide risk did not vary according to age; offspring were similarly

affected by parental schizophrenia regardless of whether they were adolescents or adults. This emphasizes the need for increased awareness of suicide risk and targeted interventions also for adolescent or young adult offspring of parents with schizophrenia.

Previous research suggests that mothers with schizophrenia may exert an additional effect on their daughters' suicide risk (Webb *et al.* 2007), and, on the contrary, an excess risk of suicidal behavior has further been found among offspring of fathers with schizophrenia (Webb *et al.* 2007). However, our quite well-powered study found no differential risk based on the gender of the parent hospitalized for schizophrenia. Even though systematic knowledge about the effects of fathers with schizophrenia on offspring is sparse (Ramchandani & Psychogiou, 2009), our results indicate that paternal schizophrenia should not be neglected in the assessment of offspring suicide risk.

We were able to adjust for several important predictors of offspring suicide. The estimates were also controlled for environmental mechanisms, for example, imitation of suicidal behavior in the family and transmission of mental illness, previously suggested as possible explanations for the increased suicide risk in offspring of schizophrenic parents (Brent & Mann, 2005). After adjustment for education, parental suicidal behavior and offspring mental illness, the suicide risk among offspring of parents with schizophrenia remained increased.

Strengths and limitations

The strengths of the present study include the use of interlinked, longitudinal population-based registers with excellent coverage. This makes it possible to study the total Swedish population and avoid misclassification due to recall bias. Further, the accuracy of the schizophrenia diagnoses in registers has previously been found to be high (Ekholm *et al.* 2005). Because we used a definition of severe schizophrenia, which requires admission, the level of selection bias is considered minimal. Register data also have limitations such as left truncation (lack of information before register start) and right censoring (inability to follow individuals after the end of register follow-up). We handled these limitations by matching on birth year to ensure that cases and controls had equivalent time at risk to enter registers and by restricting offspring births to 1996 to ensure a minimum age of at least 12 years at the end of the follow-up in 2008. However, we could not avoid possible misclassification due to the use of register data. The amount of suicidal behavior might be underestimated, because not all suicide attempts are recorded in registers, and completed suicides might be misclassified as other

causes of death. However, we believe possible misclassification to be non-differential by parental mental illness, thus it should not substantially bias our OR estimate. Similarly, schizophrenia and other mental illness defined on the basis of hospitalization limits the assessments to those who receive in-patient treatment. Nevertheless, because Sweden has a universal, tax-financed health-care system that ensures equal access to in-patient care, a treated sample is probably representative.

Further, the effect of parental schizophrenia on offspring suicide risk might be affected by how long they lived together. Thus, more information regarding change of offspring residence would have been desirable. Some of the factors adjusted for in the analyses, such as offspring mental illness, might mediate the effect of parental schizophrenia on offspring suicidal behavior. Adjusting for such factors could introduce bias of the estimated risk if unmeasured confounders are present in the association between the mediating factor and offspring suicide. However, this is unlikely to fully explain the environmentally mediated increased suicide risk in offspring of parents with schizophrenia.

In conclusion, we find a doubled risk of suicidal behavior among offspring of parents hospitalized for schizophrenia. This increased risk persists up to the age of 30 years, and is independent of the gender of the schizophrenic parent and if suicidal behavior is divided into attempted *versus* completed suicide. Our results indicate that the doubling in offspring suicide risk is at least partly due to environmental mechanisms related to having a schizophrenic parent. These findings should inspire increased attention also to suicidal ideation and prevention efforts in adolescent and adult offspring of parents with schizophrenia. Further research is needed to delineate what environmental risk factors and mechanisms should be targeted with appropriate psycho-educational, psychotherapeutic or even pharmacological interventions to decrease this risk.

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Declaration of Interest

None.

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