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The Association Between Parental Schizophrenia and Offspring Suicide: A Cousin Comparison approach

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Abstract

Objectives—This study evaluated the suicide risk among offspring of parents hospitalized for schizophrenia and elucidated the mechanisms behind this association.

Methods—We applied a nested case-control design based on a linkage of Swedish population-based registers. Among 12- to 30-year old offspring, we identified 22 850 suicide cases and their parents. For each case-parent pair we matched five healthy controls-parent pairs. All individuals were followed up to the end of 2004. We performed conditional logistic regression models to estimate adjusted odds ratios. To disentangle familial confounding from environmental mechanisms we also compared the population based suicide risk with the observed risk within full-cousins and half-cousins differentially exposed for parental schizophrenia.

Results—Offspring of parents with schizophrenia had a significantly increased risk of suicide after accounting for socioeconomic status, parental suicide and offspring mental illness (odds ratio 1.73 [1.47–2.04]). The suicide risks in offspring of schizophrenic mothers and schizophrenic fathers were similar in magnitude. The suicide risk was also similar across different developmental periods. The offspring of siblings discordant for schizophrenia showed comparable odds ratios within full cousins (odds ratio 2.02 [1.48–2.76]), and within half-cousins (odds ratio 2.03 [0.96–4.28]).

Conclusions—Parental schizophrenia is associated with an increased risk for offspring suicide. The suicide risk in offspring remained unchanged when comparing genetically different relationships, which indicate that parental schizophrenia acts directly through environmental mechanisms. These findings highlight the importance of increased social support to offspring of parents with schizophrenia in order to prevent suicidal events.

Introduction

Offspring of parents hospitalized for psychiatric disorders are at increased risk of death from unnatural causes (Webb et al. 2007; Chen et al. 2010, Hiroeh et al. 2001). In particular, findings indicate an increased risk of suicide among offspring of parents with schizophrenia

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(Mittendorfer-Rutz et al. 2008; Stenager and Qin, 2008). However, little is known about the mechanisms underlying this association. It is unclear whether potential risk factors for offspring suicide act directly through environmental mechanisms or if the association is due to a common genetic susceptibility for schizophrenia and suicide. In addition, it is not known whether there are different periods of life where suicide risk is especially elevated, whether the risk for offspring suicide is independent of the mothers' or the fathers' diagnosis of schizophrenia, and whether socioeconomic status and potential covariates account for the association. Thus, a better understanding of the mechanisms underlying the association between offspring suicide and parental schizophrenia is important to target intervention efforts.

Family studies have indicated that genetic factors are important in nearly all mental illnesses (Kendler et al. 2003). In particular, offspring of parents with schizophrenia have a higher genetic liability of developing these illnesses themselves (Lichtenstein et al. 2009; Gottesman & Bertelsen, 1989). A recent finding also indicated that nearly 80% of all suicide attempters have a prior mental disorder (Nock et al. 2010). Consequently, if parental schizophrenia and offspring suicide are influenced by the same genetic effects, the shared genetic liability would create an increased risk of suicide among offspring of schizophrenic parents. Besides possible genetic mechanisms, suicide risk in offspring could also be increased through mentally ill parents' influence on the family environment (e.g. impaired care for their children) (Johansson et al. 2002, Gould et al. 1996). Individuals diagnosed with schizophrenia have also higher rates of risk environments, such as completed suicide in relatives (Palmer et al. 2005) and violence in the family (Brennan et al. 2000), which have been suggested to increase the occurrence of suicide events in offspring (Brent et al. 2005, Johansson et al. 2002). Thus, both genetic and shared environmental mechanisms might influence the association between offspring suicide and parental schizophrenia.

The objective of this study was to evaluate the suicide risk among offspring of parents with severe schizophrenia (i.e. hospitalized with the presence of delusions, hallucinations or other psychotic symptoms) and, if considered present, to disentangle the mechanism behind this association. These mechanisms were studied using both measured covariates to control for several central predictors of offspring suicide in relation to parental schizophrenia and using a quasi-experimental approach by comparing the suicide risk in offspring differentially exposed for parental schizophrenia. We had three secondary objectives. First, we aimed to explore whether the risk of suicide among offspring of patients with schizophrenia is more pronounced in specific periods of life. Increased risks of death due to unnatural causes in preschool children (Webb et al. 2007; Chen et al. 2010) and suicide in early adulthood (Webb et al. 2007) have been shown among offspring of parents with mental illness, but due to small samples very little is known about suicide risk in adolescence (Webb et al. 2005). Second, we aimed to explore if the risk differed for maternal and paternal schizophrenia. Specifically, little is known about the risk of suicide among offspring of fathers with schizophrenia (Ramchandani & Psychogiou, 2009). Previous studies have suggested that the association between parental caregiving and child behavior is stronger for maternal compared to paternal behavior, which have been suggested to be caused by the fact that in most families mothers were the primary caregiver and thus more involved in handling their children's problems. (Rothbaum & Weisz, 1994; Rothbaum, F., & Weisz, J. R. (1994). Parental caregiving and child externalizing behavior in nonclinical samples: a meta-analysis. *Psychological Bulletin*, 116(1), 55–74.).

Some studies have found evidence of increased levels of suicide in daughters of mothers with schizophrenia (Stenager and Qin, 2008), while others have found higher suicide risk especially in offspring of schizophrenic fathers (Webb et al. 2007). Thus, it is unclear

whether the risk of suicide in offspring differs between mothers and fathers with schizophrenia.

Thirdly, we investigated the influence of potential risk factors underlying the association between offspring suicide and parental schizophrenia. Suicide risk has been strongly associated with socioeconomic factors (e.g. low income, unemployment and disability) (Qin et al. 2003). Nevertheless, previous studies have not adequately adjusted for socioeconomic factors in the assessment of offspring suicide risk (Webb et al. 2006; Webb et al. 2007). The association between offspring suicide and parental schizophrenia could also be mediated by covariates such as a family history of suicide (Qin et al. 2002; Brent et al. 2002; Lieb et al. 2005), and offspring mental illness (Qin and Nordentoft 2005). Specifically, affective disorders and substance abuse disorders have been shown to have an impact on suicide risk (Qin and Nordentoft, 2005). The contributions of these potential mediators were assessed by adjusting for these factors individually.

Method

Data sources

The present study is based on a record linkage with five different registers, where the personal identification number, unique for all residents in Sweden, makes it possible to link several population-based registers.

The Swedish Multi-Generation Register (MGR, Statistics Sweden), includes all children (index persons) born since 1932 and their biological or adoptive parents. 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) are registered in the **National Patient Register** from 1973 and onward. The **Cause of Death Register** (with data for the years 1969–2004) includes all deceased persons registered in Sweden at the time of death with information on the underlying cause of death and multiple contributory causes of death. Information on highest attained educational level is recorded in the **Education Registered** since 1985, and dates of all emigration and immigration since 1969 are found in the **Migration Register**.

Subjects

We linked the index persons in the Multi-Generation register with their known biological mother and father. The study base was restricted to births before December 31, 1992, to make sure that all offspring would be at least 12 years at the end of the follow-up 2004, which resulted in almost 11-million unique child-parent relationships.

Cases were selected as singleton births, aged 12–30 years, which had either committed suicide or attempted suicide and whose parents were born in Sweden. We excluded twins and individuals with younger siblings that had committed suicide. To reduce possible misclassifications, we also excluded suicide events in children younger than 12 years. In all, our study includes 22 850 unique suicide cases.

For each suicide case-parent pair we matched 5 pairs of offspring-parent controls. Eligible as controls were index persons who had not died, emigrated, or attempted suicide at the year of the cases suicide event. The controls were matched on birth year, sex, and country of birth of the suicide case and on birth year and sex of the parent.

Measures

Outcome - Offspring Suicide—Suicide events were defined as committed suicides (ICD8 and ICD9: E950-E959, ICD10: X60-X84) in the Cause of Death register or attempted suicides (ICD8 and ICD9: E980-E989; ICD10: Y10-Y34) as main-diagnoses or secondary-diagnoses in the National Patient Register.

Exposure - Parental Schizophrenia—Schizophrenia was defined hierarchically according to the discharge diagnoses (ICD8 and ICD9: 295; ICD10: F20). That is, we allowed for co-occurring syndromes of bipolar disorder (ICD8: 296.1, 296.3, 296.8; ICD9: 296A, 296C-E, 296W; ICD10: F30-F31). We excluded any type of schizophrenia that included episodes of non organic psychotic symptoms. Validation studies have indicated low number of false-positive diagnoses of schizophrenia in Swedish registers (Ekholm et al. 2005).

Covariates—Socioeconomic status (SES) was considered a confounder for the association between offspring suicide and parental schizophrenia, and was adjusted for in the analyses. SES was assessed by highest attained education level in the index person and 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).

We further measured the contribution of potential mediators by adjusting for parental suicide and offspring mental illness in the analyses. Parental suicide was defined using the same criteria as for offspring suicide. Also, we only considered offspring as exposed to parental suicide if their suicide occurred before the offspring suicide.

Offspring mental illness was defined as any admission of schizophrenia, affective disorders (including bipolar disorder), alcohol/drug related disorders, or other psychiatric diagnoses (ICD8: 291, 295, 296.0–296.3, 296.8–296.9, 297–301, 303, 304; ICD9: 291–292, 295, 296A–296E, 296W–296X, 297–298, 300–301, 303–304, 305X, 311; and ICD10: F10–F25, F28–F31, F32.0–F32.3, F32.8–F32.9, F33–F42, F44–F45, F48, F60–F62) measured before the offspring suicide and for the control offspring before the suicide of the matching case offspring.

Statistical analyses

Case-Control Design—First, we used conditional logistic regression models to calculate odds ratios (OR) with 95% confidence intervals. Analyses were performed in SAS 9.22 using the phreg procedure (SAS Institute, Inc., Cary, NC). We fitted crude models and three differently adjusted models. Odds ratios from the crude analyses were adjusted for birth year, sex, and country of birth of the suicide case and on birth year and sex of the parent through matching. We consecutively adjusted for potential effect of SES, parental suicide and offspring mental illness to examine the distinctive effect from the respective risk factors.

In subgroup analyses, we stratified suicide events by offspring age as 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 accomplishes formal education up to this age in Sweden; also legal adulthood and adult psychiatric care both take effect at age 18. Young adults were stratified into two parts to explore potential differences during the development. Age 30 years was chosen as the maximum cut-off point since the effect of parents with mental illness is most likely reduced at higher ages. Additionally, the analyses were stratified by parental gender.

Cousin Comparison Design—Secondly, to study possible familial confounding we also applied cousin comparison analyses. We used the population based registers to identify all parental-sibling pairs (both full siblings and half-siblings) discordant for schizophrenia where both members of the pair had at least one offspring. To resemble the sample from the case-control analyses we only included sibling pairs where offspring was born before the end of 1992. We excluded twins since monozygotic twins are genetically identical and their children (who are cousins) would have the same genetic resemblance as half-siblings. Each parental sibling was only allowed to occur once in the sample. Thus, in families with odd number of 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, we included 4464 unique sibling pairs discordant for schizophrenia and their children in the sibling comparison analyses. In accordance with this approach we obtained the reference odds ratio by using the nested case-control design with schizophrenic parents as our cases.

We explored the importance of familiar risk factors for the association between offspring suicide and parental schizophrenia by comparing the risk of suicide within full cousins, and half-cousins (whose parents are half-siblings) differentially exposed for parental schizophrenia. Assuming an increased risk for suicide in offspring to patients with schizophrenia in the case-control study, there could be two different patterns of results in the sibling comparison analyses.

First, if the risk of suicide within differentially exposed cousins and half-cousins remains at the same level as the risk in the population this would indicate an environmental association. That is, if there is an environmental association, these analyses would give a risk comparable to the case-control study. Second, if the risk of suicide within differentially exposed full cousins diminishes compared to the risk in half-cousins, the results would indicate that the association is confounded by genetic mechanisms. Specifically, if offspring suicide and parental schizophrenia are influenced by the same genetic effects, we would expect offspring of the schizophrenic parents (of a discordant sibling pair) to inherit some susceptibility genes from their parents resulting in a high risk of suicide. Likewise, if genetic effects are of importance we expect a moderate risk of suicide in offspring of the healthy parent as these children also inherit some part of the susceptibility genes indicating a moderate risk of suicide. Correspondingly, if genetic effects are important for the associations we expect the suicide risk among half-cousins differentially exposed for parental schizophrenia to be markedly attenuated compared to the overall risk in the general population. The study was approved by the Ethics Committee at Karolinska Institutet.

Results

Descriptive statistics

We identified 22 850 suicide cases (60% males and 40% females) aged 12–30 years, born between the years 1939 to 1992. Linking the suicide cases with their known biological mother and father resulted in 40 290 offspring-parent pairs and 195 105 matched offspring-parent pair controls. Descriptive information separated by offspring-mother and offspring-father relationships is presented in Table 1. A fraction of all cases and controls (3.0% and 0.5% respectively) lacked information regarding education level and were excluded from the models. In general, controls had higher attained education level than cases; 38% of the controls had completed higher education compared to 21% of the cases. Similarly, 11% of the controls had attained elementary education while the corresponding number was 25% for cases. Furthermore, the prevalence of suicide was about three times higher in parents of cases compared to parents of controls. A history of offspring mental illness was more than ten times higher among suicide cases compared to controls. This indicates that offspring mental illness and offspring suicide are strongly associated.

Risk Factors

Crude and adjusted odds ratios associated with offspring suicide and parental schizophrenia are presented in the first column of Table 2. Results from the crude analysis showed a statistically significant increased risk of suicide in offspring of parents with schizophrenia (OR=2.27; 2.00–2.58). The association remained statistically significant even after adjusting for SES alone (OR=2.08; 1.82–2.37), and after further adjustment for parental suicide (OR=2.05; 1.79–2.34) and a history of offspring mental illness (OR=1.73; 1.47–2.04).

Age-stratified results (Table 2) revealed similar risk estimates across the three age group strata (with OR range from 2.07 to 2.36), suggesting that the risk associated with parental schizophrenia acts across different periods of life. Table 2 also presents the specific odds ratios associated with maternal and paternal schizophrenia. The risk of offspring suicide specific to mothers with schizophrenia was of similar magnitude to the risk specific to fathers. Thus, there was no evidence of higher suicide risks in offspring exposed to maternal compared to paternal schizophrenia.

Cousin Comparison

We identified 3919 full sibling pairs and 545 half-sibling pairs discordant for schizophrenia that fulfilled our inclusion criteria (see Table 3). For each sibling relationship, Table 3 also shows the prevalence of suicide in offspring of the unaffected siblings and of the siblings with schizophrenia. The suicide risk was, independent of familial relationship, roughly twice as high for offspring of parents with schizophrenia. Specifically, the offspring suicide risk in the total population (OR=2.01; 1.83–2.20) were comparable to the observed risk within differentially exposed full cousin pairs (OR=2.02; 1.48–2.76) and also within differentially exposed half-cousin pairs (OR=2.03; 0.96–4.28). These results suggest that the association between offspring suicide and parental schizophrenia is not confounded by familial (genetic or shared environmental) factors because the risk within each family structure was of similar magnitude.

Discussion

This is the first population based study of suicide during childhood through early adulthood among offspring of parents with schizophrenia. We observed a robust twofold increased risk across different periods of life for this association, which is in line with several studies investigating the association between parental schizophrenia and unnatural causes of death (Webb et al. 2007; Stenager & Qin, 2008). We also observed a twofold increased risk of suicide in offspring of parents with schizophrenia, regardless of whether the mother or the father had the disorder. Further, the suicide risk in offspring was of similar magnitude when comparing cousin pairs differentially exposed for parental schizophrenia. Thus, our results suggest that the association between parents with schizophrenia and offspring suicide is due to environmental mechanisms, and not due to genetic confounding.

Genetic and Environmental Effects

Although earlier findings have demonstrated that suicidal behavior runs in families (Brent et al. 2005) the mechanisms underlying the association between suicidal behavior in offspring and severe parental mental illness have not been clarified. We found that the risk of suicide within cousins differentially exposed for parental schizophrenia remained at the same level regardless of parental sibling relatedness. Since the strength of the effect remained unchanged when comparing genetically different relationships these results indicate that the association is not confounded by genetic factors. 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 (Johansson et al. 2002) are important risk factors for suicidal behavior in offspring. Such parental behaviors and traits tend to increase the offspring's introverted behavior, which contributes to avoidance of social contacts, desperation, hopelessness and most likely later suicidal behavior (Bridge et al. 2006). Parents with recent admission of a severe mental disorder have an increase risk of suicide themselves (Dutta et al. 2010), and might also have trouble focusing on the psychological health of their offspring, which could increase the levels of suicide in these families. In addition, a recent study reported higher risks of suicide in offspring the more recent a parent had been admitted for mental illness (Stenager & Qui, 2008). Their findings likewise suggest that suicide events in offspring are most likely influenced by parental mental illness through emotional and environmental effects rather than via a shared genetic basis (Stenager & Qui, 2008).

Our findings showed that the risk for offspring suicide did not vary according to age (i.e. offspring are similarly affected by their parents' attitudes regardless of whether they are adolescents or adults). These findings emphasize the need for intervening with offspring of parents with schizophrenia (e.g., providing social support), regardless of whether they are adolescents or young adults.

We found no differences in the association between suicides in offspring of fathers with schizophrenia compared to offspring of mothers with schizophrenia. Despite some evidence that mothers with schizophrenia may have an additional effect on daughters suicide (Stenager and Qin, 2008), the suicide risk in offspring were of similar magnitude for mothers and fathers hospitalized for schizophrenia. Even though knowledge of fathers with schizophrenia has been sparse (Ramchandani & Psychogiou, 2009), these results indicate that paternal schizophrenia should not be neglected in the assessment of suicide risk in offspring. Even though mothers most often are the primary caregiver (Rothbaum & Weisz, 1994) the similar influence of maternal and paternal schizophrenia on offspring suicide suggest that a direct environmental mechanisms such as schizophrenics' inadequate parental care. It should be noted that this association is in contrast with a Danish register-based study who reported an excess risk of suicide among offspring of fathers with schizophrenia. However, their reported risk may be uncertain due to small number of suicide cases (n=8) (Webb et al. 2007).

We were able to adjust for several important predictors of offspring suicide. The estimates were also controlled for environmental mechanisms such as imitation of suicidal behavior in the family and transmission of mental illness that have earlier been suggested to be possible explanation for the increased risk of suicide in offspring of schizophrenic parents (Brent et al. 2005). Having adjusted the odds ratios for SES, parental suicide, and offspring mental illness, the population based risk for offspring suicide of parents with schizophrenia were still strongly increased (OR=1.73).

The strengths of the present study are the use of population based registers which makes it possible to follow the total Swedish population and to remove misclassification due to recall bias. Further, the accuracy of the schizophrenia diagnoses in the Swedish register has previously been reported as generally high (Ekholm et al. 2005). Because we used a definition of severe schizophrenia, which requires admission, the level of selection bias is considered minimal. However, register data also have limitations in form of left truncation (lack of information before register start) and right censoring (unable of following individuals after the end of register follow-up). We handled these limitations by matching on birth year to make sure that cases and control pairs had equivalent time at risk to enter the registers and by restricting offspring births to 1992 to enable an age of 12 years at the end of the follow-up 2004. Some of the factors adjusted for in the analysis might mediate the effect

of parental schizophrenia on offspring suicide e.g. offspring mental illness and parental suicide. 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, the possibility that the high suicide risk in offspring of parents with schizophrenia would be fully explained by confounders of eventual backdoor paths (opened by adjusting and not accounted for in the analyses) seem doubtful.

In conclusion, there is an increased risk of suicide among offspring of parents with schizophrenia. Secondly, the increased risk persists into adulthood, and is independent of the sex of the schizophrenic parent. The results also reveal that this association is not due to genetic confounding, but rather environmental mechanisms. These findings highlight the importance of targeting intervention efforts at parents with schizophrenia and increase the social support to their offspring in order to prevent suicidal events.

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Table 1

Identified cases and controls and the distribution of confounders

	Number (% of total)	
	Case pairs	Control pairs
Relationship		
Offspring-Mother	20 960	101 422
Offspring-Father	19 330	93 683
Total	40 290	195 105
Highest attained education level		
Elementary education (< 9 years)	10 131 (25.2)	21 870 (11.2)
Secondary education (10–12 years)	20 521 (50.9)	98 494 (50.5)
Higher education (> 13 years)	8 436 (20.9)	73 710 (37.8)
Missing data	1 202 (3.0)	1 031 (0.5)
Parental suicide	130 (0.3)	220 (0.1)
Offspring mental illness	7 795 (19.4)	2 345 (1.2)

Table 2

Overall and age-specific risk of suicide in offspring of schizophrenic parents combined and for mothers and fathers separately.

	Number of pairs		OR (95% CI)			
	Cases	Controls	Crude ^a	Adjusted ^b	Adjusted ^c	Adjusted ^d
Parents						
Total	39088	194074	2.27 (2.00–2.59)	2.08 (1.82–2.37)	2.05 (1.79–2.34)	1.73 (1.47–2.04)
Adolescents (12–18 y)	9171	44748	2.36 (1.80–3.10)	2.19 (1.66–2.88)	2.09 (1.58–2.75)	1.99 (1.49–2.65)
Young adults (19–25y)	18062	89388	2.10 (1.73–2.55)	1.77 (1.44–2.82)	1.75 (1.43–2.16)	1.58 (1.23–2.01)
Adults (26–30y)	11856	59859	2.20 (1.75–2.76)	1.99 (1.58–2.51)	1.98 (1.57–2.50)	1.52 (1.13–2.06)
Mothers						
Total	20469	100888	2.28 (1.94–2.68)	2.08 (1.76–2.45)	2.03 (1.71–2.39)	2.00 (1.38–2.90)
Adolescents (12–18 y)	4698	22825	2.46 (1.74–3.47)	2.25 (1.59–3.18)	2.05 (1.35–3.24)	2.11 (1.60–2.79)
Young adults (19–25y)	9403	46192	1.88 (1.48–2.40)	1.60 (1.23–2.07)	1.57 (1.21–2.04)	1.45 (1.06–2.00)
Adults (26–30y)	6369	31899	2.37 (1.81–3.10)	2.11 (1.60–2.79)	2.10 (1.59–2.77)	1.63 (1.13–2.35)
Fathers						
Total	19330	93683	2.26 (1.82–2.80)	2.07 (1.67–2.58)	2.08 (1.67–2.58)	1.78 (1.38–2.30)
Adolescents (12–18 y)	4473	21923	2.22 (1.44–3.44)	2.11 (1.36–3.25)	2.09 (1.35–3.24)	1.92 (1.22–3.03)
Young adults (19–25y)	8659	43196	2.58 (1.88–3.56)	2.13 (1.52–3.00)	2.15 (1.53–3.02)	1.84 (1.27–2.66)
Adults (26–30y)	5487	27960	1.86 (1.23–2.80)	1.75 (1.16–2.62)	1.75 (1.16–2.62)	1.29 (0.79–2.13)

^aCrude estimates were adjusted for sex, age and country of birth through matching

^bThe estimates were further adjusted for socioeconomic status (SES)

^cThe estimates were further adjusted for SES and parental suicide

^dThe estimates were further adjusted for SES, parental suicide, and offspring mental illness.

Table 3

Prevalence of suicide in offspring of siblings pairs discordant for schizophrenia.

Prevalence of suicide in offspring of discordant parents				
Parental Relationship	Pairs	Schizophrenic (No.)	Unaffected (No.)	OR (95% CI)
Total Population				2.01 (1.83–2.20)
Full Siblings	3919	1.47 (107)	0.73 (64)	2.02 (1.48–2.76)
Half Siblings	545	1.92 (19)	0.96 (11)	2.03 (0.96–4.28)

Abbreviation: CI, confidence interval.