

Sibling aggregation for psychiatric disorders in offspring at high and low risk for depression: 10-year follow-up

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ABSTRACT

Background. A unique way of determining patterns of parent–offspring transmission of risk to affective disorders is to focus on aggregation within sibling pairs. We attempt to extend our previous finding that sibling aggregation is notable for anxiety disorders in a 10-year follow-up of siblings at high and low risk for depression, by virtue of parental diagnosis.

Methods. The sample, which included 173 unique sibling pairs in the high risk cohort, and 83 pairs in the low risk cohort, had been assessed using semi-structured clinical interviews three times over a 10-year period, spanning from childhood to adulthood. Sibling aggregation was quantified using pairwise odds ratios.

Results. Sibling aggregation in the high risk cohort was greater than aggregation in the low risk cohort for anxiety disorders, especially those that emerged in childhood, and later co-morbid disorders, especially major depressive disorder and suicide attempts.

Conclusions. Familial liability to affective disorders may be reflected most strongly by a developmental sequence of anxiety disorders in childhood followed by later depressive and suicidal behaviour in adolescence and adulthood.

INTRODUCTION

Offspring of depressed parents have been shown consistently to have higher rates of psychiatric disorders than offspring of non-depressed parents. However, a key issue, yet to be resolved, is the specificity of parent–offspring transmission, as offspring of depressed parents have heightened rates of many disorders, including depressive, anxiety and conduct disorders (Weissman *et al.* 1987, 1991, 1997; Hammen *et al.* 1990). Hence, it is not clear whether high-risk offspring are vulnerable to psychopathology in general, or rather to more cleanly carved forms of dysfunction (such as particular developmental sequences of core disorders). The lack of well-

defined boundaries of the most prominent forms of dysfunction in offspring at risk obfuscates the search for aetiological mechanisms such as genetic factors, which require precise definitions of the key features of the disease phenotype (Merikangas, 1993).

Sibling aggregation in the high-risk paradigm

One approach that has been used to sharpen the focus on the boundaries of psychopathology in offspring at risk is to examine sibling aggregation. Although high-risk studies traditionally have focused on analysing individual rates of disorders, many studies include multiple observations per family (i.e. siblings). Such dependency in family studies, though typically regarded as a statistical complication (violation of assumption of independence of observations), provides a unique opportunity to determine

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aggregation for psychiatric disorders within families (Rende & Weissman, 1999a). For example, Rende *et al.* (1995) have demonstrated that a given hypothetical aggregate rate of affected offspring (e.g. 50%), calculated at the level of individuals, can arise from multiple patterns of sibling aggregation, ranging from complete discordance (i.e. no aggregation at the level of siblings) to complete concordance (i.e. perfect aggregation at the level of siblings). Hence, as high-risk studies may include siblings, analytical methods aimed at determining sibling aggregation avoid violations of assumptions of independence, and may reveal more clearly how psychopathology aggregates within families (which cannot be inferred when dependent cases are treated as if they are independent observations).

We have applied an analytical method derived from genetic epidemiology, the pairwise odds ratio (Khoury *et al.* 1993), to assess sibling aggregation in offspring at high and low risk for depression by virtue of parental diagnostic status (Rende *et al.* 1995). Our preliminary findings suggested that the magnitude of sibling resemblance for depression was very similar for the high and low risk cohorts, suggesting that the common or shared familial influences impacting the development of depression in multiple children in a family are not more 'powerful' in families at high risk due to parental depression. The notable distinction between the high and low risk cohorts, in terms of sibling resemblance, was found for anxiety disorders and disorders (including depression) co-morbid with anxiety disorders. This suggests that familial liability to psychopathology in offspring of depressed parents may be reflected most strongly through anxiety rather than affective disorders. The primary limitation to these findings was that many of the siblings had not passed through the age of first onset for the disorders under investigation, especially depression, suggesting the need for longitudinal assessments to determine more precise estimates of sibling aggregation for lifetime history of psychiatric disorders.

Goals of the present study

The overall goal of this paper is to extend our findings on sibling aggregation for psychiatric disorders (Rende *et al.* 1995) by focusing on the

sample as they have participated in a 10-year follow-up study (Weissman *et al.* 1997). As most subjects have passed through the age of risk for first onset of disorders, we will determine more definitive estimates of sibling aggregation for lifetime rates of disorders, including major depressive disorder, anxiety disorders, drug and alcohol abuse, and suicide attempts.

The following key questions will be addressed: (1) Which disorders aggregate most strongly in siblings at high risk for depression, as compared to siblings at low risk?; (2) Are there notable age or gender effects on sibling aggregation?; (3) Are there patterns of co-morbidity that underlie sibling aggregation for psychiatric disorders?; and (4) Is sibling aggregation associated with patterns of co-morbidity in parents?

METHOD

Sample

Offspring were initially selected for the presence or absence of a lifetime history of major depression (based on Research Diagnostic Criteria) in their parents. A complete description of the probands (parents) and the assessment has been published elsewhere (Weissman *et al.* 1997). The depressed probands had received treatment at Yale University Depression Research Unit (New Haven, CT). The normal controls came from a 1975 community survey conducted in New Haven. They had no history of psychiatric illness, based on at least four direct interviews. The last two interviews used the Schedule for Affective Disorders and Schizophrenia - Lifetime Version (SADS-LA) (Mannuzza *et al.* 1986). All probands were white and group matched for age and sex.

At the initial interview (Time 1), the sample consisted of 220 offspring between ages 6 and 23 years from 91 families, 153 offspring from 65 families with one or more depressed parents and 67 offspring from 26 families with neither parent depressed (see Weissman *et al.* 1997). Two years after the initial interview (Time 2), all 91 families were contacted for a second interview. Eighty-five (93%) of the 91 families consented to participate. Of the 220 offspring interviewed at Time 1, 174 (79%) of them were re-interviewed at Time 2 (Weissman *et al.* 1997). An additional sample of 43 offspring who were not age eligible at Time 1 were interviewed also. Ten years after

the initiation of the study (Time 10), families were recontacted for a reassessment. Two-hundred and seventeen offspring were eligible to be interviewed at Time 10; 84% (182/217) of those offspring (interviewed at Time 1) were re-interviewed (Weissman *et al.* 1997). Attrition of offspring did not differ by parental status or sex. However, at Time 10, older offspring were more likely to be interviewed than younger offspring (mean 28.5 v. 26.4 years of age; $P < 0.05$). The age range of offspring at Time 10 was 16–38 years; the median age was 28.3 years. There were two first onsets of major depression in the spouses of the non-depressed group between Time 2 and 10. We reassigned these families to the parent depressed group.

In this report analyses are based on the subsample of families that contributed more than one offspring to the study: 80.7% of the families in the high risk sample, and 86.4% of the families in the low risk sample. In the high risk sample, a total of 173 unique pairs (see below) of siblings (58 female–female, 90 female–male, 25 male–male) were available for analyses; 83 pairs of siblings (28 female–female, 39 female–male, 16 male–male) were available in the low risk sample.

Assessment

Offspring were directly and independently interviewed with the Schedule of Affective Disorders and Schizophrenia-Lifetime version (SADS-LA) modified to include RDC, DSM-III and DSM-III-R criteria. The period of assessment was from the last time of interview until the present, yielding, across all three timepoints, a lifetime history of psychiatric disorders (Weissman *et al.* 1997). Interviewers included Ph.D. and Masters-level experienced mental health professionals and were located in Connecticut where most of the subjects lived. Each month we required that all interviewers do joint interviews: one interviewer conducted the interview and the other co-rated the interview. Using probable or definite DSM-III-R criteria, kappa coefficients for the major categories ranged from 0.65 for anxiety disorders to 0.96 for drug abuse or dependence.

Best estimate diagnosis

Diagnoses of offspring were based on the Best Estimate (BE) procedure (Leckman *et al.* 1982). Using probable or definite DSM-III-R criteria,

kappa coefficients for major diagnostic categories ranged from 0.68 for any anxiety disorder to 0.92 for alcohol abuse or dependence; details of the methods can be found elsewhere (Weissman *et al.* 1997). In this report, we focus on lifetime history of five disorders with relatively high prevalence in the present sample: major depressive disorder, anxiety disorders, drug abuse, alcohol abuse and suicide attempts.

Statistical analysis

Sibling resemblance for each disorder was determined using the pairwise odds ratio, which is analogous to the intra-class correlation coefficient for a dichotomous variable (Hunt *et al.* 1986). The pairwise odds ratio for any two siblings is defined as follows: it is the ratio of the odds that, given that any sibling selected at random (from the set of siblings within a family) has the disorder, a second sibling selected at random will also have the disorder, over the odds that, given that any sibling selected at random does not have the disorder, a second sibling picked at random will have the disorder. A formula for calculating the pairwise odds ratio is as follows, based on categorizing each sibling pair into concordant (both sibs affected) and discordant (one sib affected) pairs: if the number of concordant pairs is X , the number of discordant pairs is Y and the total number of pairs is N , then the odds ratio is $(2.X/Y)/(Y/2.(N-X-Y))$ (Rende *et al.* 1995).

The pairwise odds ratio is computed using all possible pairs of siblings within a family (Khoury *et al.* 1993); hence a sibship of 3 would contribute three unique pairs. Such 'multiple counting' of individuals does not produce biased test statistics, because '...if sibs are truly independent of one another in risk, it will not matter if any one sib appeared in several pairs when constructing the final table' (Khoury *et al.* 1993, p. 190). Hunt *et al.* (1986) present a mathematical demonstration that, in the case of intraclass aggregation (such as aggregation within sibships), the pairwise odds ratio and the corresponding chi-square statistic are not biased. This property of the pairwise odds ratio makes it a more suitable analytical technique than other non-parametric indices such as concordance, which assumes only two observations per family as in the case of twins (Rende *et al.* 1995).

An odds ratio > 1 indicates that the diagnostic status of one sibling is dependent on the diagnostic status of a second sibling; the significance of such sibling aggregation is tested using the traditional chi-square statistic (Hunt *et al.* 1986).

RESULTS

Which disorders aggregate most strongly in siblings at high risk for depression, as compared to siblings at low risk?

Table 1 presents descriptive data on sibling concordance along with the pairwise odds ratios (with 95% confidence intervals) for the five disorders of interest. Sibling aggregation was significant for four of the five disorders in the high risk sample. Most notable was aggregation for anxiety disorders and for suicide attempts. Although the pairwise odds ratio for suicide attempts exceeded that for anxiety disorders, there were only 10 sibling pairs concordant for suicide attempts, as compared to 60 pairs concordant for anxiety disorders (which is reflected by the much wider confidence interval for the pairwise odds ratio for suicide attempts as compared to that for anxiety disorders). Sibling aggregation for anxiety disorders was due to aggregation for separation anxiety, simple phobias, and social phobias; the sample size was too small to generate meaningful pairwise odds ratios for these specific anxiety disorders.

In contrast, sibling aggregation was negligible for four of the five disorders in the low risk sample, with the exception being major depressive disorder, for which the pairwise odds ratio of 1.91 was comparable to that found in the high risk sample (as also indicated by the

similar confidence intervals). As demonstrated by a comparison of the 95% confidence intervals, high risk sibships may be most strongly discriminated from low risk sibships by aggregation for anxiety disorders, and suicide attempts. The pairwise odds ratios indicated as ' < 1 ' for sibling pairs in the low risk sample reflect independence between siblings for low base rate disorders (i.e. the asymmetry in the cells of interest were too extreme to calculate meaningful odds ratios and corresponding confidence intervals).

Are there notable gender or age effects on sibling aggregation?

Table 2 presents the pairwise odds ratios for siblings in the high risk cohort, separately by gender composition. Although sibling aggregation for anxiety disorders is detectable for all gender compositions, the impact of gender is easily seen by the increase in the pairwise odds ratios corresponding to the number of females in each sibling pair. Sibling aggregation is also strongest in sister pairs for major depressive disorder and suicide attempts; no gender effects were observed for drug and alcohol abuse. There were negligible gender effects for aggregation for major depressive disorder in the low risk sample (not shown in Table 2).

The possible impact of age on sibling aggregation was investigated in two ways. First, the sample of sibling pairs was stratified by age (those in which both siblings were 30 years or older, and those in which both siblings were under 30 years), and pairwise odds ratios computed for the stratified samples. Using this approach no notable differences in the pairwise odds ratios were found. Secondly, rather than

Table 1. Sibling aggregation for lifetime history of psychiatric disorders in offspring at high and low risk for depression

| Disorders | High risk cohort | | | Low risk cohort | | |
|---------------------------|----------------------|----------------------|-----------------------|----------------------|----------------------|------------------|
| | Concordance N (%) | Discordance N (%) | OR (95% CI) | Concordance N (%) | Discordance N (%) | OR (95% CI) |
| Anxiety disorders | 60 (34.7) | 54 (31.2) | 4.86 (2.29–9.87)*** | 2 (2.4) | 27 (32.5) | < 1 † |
| Major depressive disorder | 63 (36.4) | 68 (39.3) | 2.29 (1.27–4.57)** | 10 (12.0) | 30 (36.1) | 1.91 (0.69–5.31) |
| Alcohol abuse | 16 (9.2) | 64 (36.9) | 1.45 (0.71–3.04) | 1 (1.2) | 23 (27.7) | < 1 † |
| Drug abuse | 11 (6.3) | 49 (28.3) | 2.07 (1.08–4.90)* | 0 (0.0) | 23 (27.7) | < 1 † |
| Suicide attempts | 10 (5.8) | 21 (12.1) | 12.88 (4.44–41.68)*** | 1 (1.2) | 8 (9.6) | < 1 † |

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

† Meaningful odds ratios with appropriate confidence intervals could not be computed because of low concordance rates.

Table 2. Sibling aggregation for lifetime history of psychiatric disorders in offspring at high risk: effects of gender composition

| Disorders | Pairwise odds ratio (95% CI) | | |
|---------------------------|------------------------------|-----------------------|-----------------------|
| | Female-female (N = 58) | Mixed-sex (N = 90) | Male-male (N = 25) |
| Anxiety disorders | 9.69 (2.86-34.12)*** | 4.00 (1.73-10.48)** | 2.16 (0.42-11.82) |
| Major depressive disorder | 3.25 (1.72-14.18)* | 1.69 (0.52-14.18) | 1.76 (0.34-19.49) |

* P < 0.05; ** P < 0.01; *** P < 0.001.

Descriptive data on sibling concordance/discordance stratified by gender composition are available from the first author by request.

Table 3. Sibling aggregation for lifetime history of psychiatric disorders co-morbid with anxiety disorders

| Co-morbid disorders | Pairwise odds ratio (95% CI) | |
|---------------------------|------------------------------|----------|
| | High-risk | Low-risk |
| Major depressive disorder | 4.52 (2.75-12.06)*** | < 1 |
| Drug abuse | 1.32 (0.34-5.05) | < 1 |
| Suicide attempts | 16.22 (5.26-55.70)*** | < 1 |

*** P < 0.001.

Descriptive data on sibling concordance/discordance are available from the first author by request.

focusing on chronological age, the age gap between siblings was computed and the sample of sibling pairs was stratified using a median split. No impact of age gap between siblings was found (e.g. sibling pairs above the median age gap had a pairwise odds ratio for anxiety disorders of 5.60, as compared to a pairwise odds ratio of 4.14 for sibling pairs below the median age gap). There was, however, one exception, as siblings close in age were much more likely to aggregate for suicide attempts than siblings further apart in age (as indicated by a pairwise odds ratio of 20.72 v. 6.74). The small number of concordant siblings suggest caution in interpreting this finding.

Are there patterns of co-morbidity that underlie sibling aggregation for psychiatric disorders?

Given that sibling aggregation is most prominent for anxiety disorders in the high risk sample (based both on the pairwise odds ratio and the actual number of concordant sibling pairs), we investigated if sibling aggregation may be detected for disorders co-morbid with the anxiety disorders. Table 3 presents pairwise odds ratios

indicating sibling aggregation for disorders co-morbid with anxiety disorders for both the high and low risk cohorts. Significant aggregation for co-morbid presentation was found for major depressive disorder, and for suicide attempts, in the high risk cohort; there was no evidence of sibling aggregation for disorders co-morbid with anxiety disorders in the low risk cohort.

We were also interested in determining if there were typical developmental sequences, in terms of age of first onset, in the co-morbid presentation of disorders within sibling pairs. To address this issue, we examined the age of first onset for disorders within each individual who was in a concordant sibling pair (i.e. sibling pairs in which both siblings had a lifetime history of both anxiety disorders and other disorders). Nearly all subjects (94.6%) who had co-morbid presentation of anxiety disorders and major depressive disorder, and had a sibling with such co-morbid presentation, reported that anxiety disorders had an earlier onset than major depressive disorder. All of the subjects co-morbid for anxiety disorders and suicide attempts, and with a sibling with such co-morbid presentation, reported that anxiety disorders had an earlier onset. It is also noteworthy that the majority of subjects had a first onset of anxiety disorders in childhood (as the median age of first onset was about 8 years of age), in the form of either separation anxiety or simple phobias, whereas the first onsets of major depressive disorder were in early adolescence (with a median onset of about 12 years of age).

Is sibling aggregation associated with patterns of co-morbidity in parents?

A critical issue to be considered is whether the sibling aggregation for anxiety disorders is attributable to parental co-morbidity for anxiety

and depression. Although the sample size precluded detailed stratification of sibling aggregation for anxiety disorders based on parental co-morbidity, it is important to note that the sibling pairs of depressed parents without co-morbid anxiety ($N = 21$ pairs) had a concordance rate of 76.2%, as compared to a concordance rate of 39.9% for the sibling pairs of depressed parents with co-morbid anxiety disorders ($N = 152$ pairs).

DISCUSSION

The present study focused on sibling aggregation as a potentially strong indicator of familial liability to psychopathology within the high-risk paradigm. The analysis of sibling pairs suggests that there are particularly clear indicators of familial liability, primarily in the form of anxiety disorders. If one sibling had a lifetime history of an anxiety disorder, then a second sibling, chosen at random, was nearly five times more likely to also have had an anxiety disorder. This result extends the findings of our previous report (Rende *et al.* 1995) as most of the siblings have now been assessed as adults. The notable sibling aggregation for anxiety disorders is consistent with speculations that familial liability for depressive disorders may be first, and most strongly, revealed through the early expression of anxiety (Merikangas, 1993).

As we found in our preliminary study, sibling aggregation for major depressive disorder was of a similar magnitude in both the high and low risk cohorts. This finding is especially noteworthy given that most subjects have now been assessed three times, beginning in early adolescence and continuing into adulthood (hence passing through the age of risk for first onset of depression). A key difference between the cohorts, however, was that sibling aggregation for co-morbid presentation of anxiety disorders and major depressive disorders was found only in the high risk cohort. It may be that there are multiple aetiological pathways to major depressive disorder, and that a key indicator of familial risk in high risk cohorts is the developmental progression of onset of anxiety disorders, followed by onset of depressive disorders, as this was the predominant pattern found for sibling aggregation. The importance of anxiety disorders and co-morbid sequelae in

offspring at high risk for depression was also revealed through sibling aggregation for suicide attempts. Siblings not only clearly aggregated for suicide attempts, but such aggregation extended to co-morbid presentation of a previous onset of an anxiety disorder.

It is also of interest that siblings in the low risk group demonstrated independence in terms of their aggregation for disorders with the exception of major depressive disorder. This finding is not unexpected, as sibling resemblance for many behavioural traits (e.g. personality traits) in unselected samples is often quite low (Dunn & Plomin, 1990). Our analyses extend this observation to psychiatric disorders in groups at low familial risk, and support the contention that siblings without documented risk factors often show very different patterns of development. It is possible, however, to speculate that there may be common or shared familial factors within low-risk sibling pairs that promotes risk for depression, even in the absence of parental depression.

There were indications of gender effects on the magnitude of sibling aggregation, in the expected direction: the highest estimates of sibling resemblance were found for sister pairs in the high risk cohort, for anxiety disorders, major depressive disorder and suicide attempts. Two points are of interest. First, the strength of the associations in sisters indicate how potent sibling aggregation may be in offspring at high risk. Secondly, evidence for sibling aggregation may, nonetheless, be observed in both mixed gender and brother pairs, although the sample sizes after stratification for gender composition limit the conclusions that may be drawn. In contrast to gender composition, there was little evidence of age effects on sibling aggregation, which reflects the utility of the longitudinal sampling frame used in the present study. It should be noted, however, that our analyses of gender and age effects were determined using stratification of the sample (see Hunt *et al.* 1986), rather than direct modelling of these effects in the computation of the pairwise odds ratios; the development of such methods (comparable to those used in proportional hazards models) would represent a methodological advance.

Although these data provided only a limited view of the role of parental co-morbidity in

sibling aggregation, it was apparent that sibling resemblance for anxiety disorders was not attributable to parental co-morbidity, as the sibling pairs of parents with depression but no lifetime history of anxiety disorders had a higher concordance rate than the siblings of co-morbid parents. Given the over-representation of parents with co-morbid disorders, however, and the lack of other psychiatric control groups, future research should include a more balanced design of parental risk groups in order to determine the specificity of sibling aggregation of anxiety disorders. We note, however, that we have demonstrated in a sample of offspring of opiate-dependent parents that sibling aggregation for anxiety disorders was found only for the sib pairs of parents with co-morbid major depressive disorder (Rende & Weissman, 1999b).

The key speculations that may be drawn from assessing sibling aggregation in the high risk paradigm concern the issue of aetiological mechanisms. As the focus on siblings may help to clarify the boundaries of the disease phenotype transmitted within high risk families (Khoury *et al.* 1993; Rende & Weissman, 1999a), we propose that aetiological models of parent-offspring transmission consider the possibility that anxiety disorders, and the sequelae of co-morbid disorders including major depressive disorder, represent a candidate phenotype reflective of the familial liability to depressive disorder (see Merikangas, 1993). This proposition is consistent with speculations drawn from other paradigms, most notably family and twin studies of adults (Kendler *et al.* 1992, 1994, 1996; Weissman *et al.* 1993; Breslau *et al.* 1995), which have suggested that anxiety and depression may share common genetic influences. Another contribution of the analysis of sibling aggregation within the longitudinal high-risk design is that a rough picture of the developmental sequence of psychopathology may be appreciated, as common anxiety disorders in childhood reflect most strongly aggregation within the family (at the level of offspring), and also lead to sibling aggregation for later psychopathology, notably major depressive disorder and suicide attempts.

Although the high-risk paradigm cannot disentangle genetic and non-genetic sources of influence (Rende & Plomin, 1995), the findings of this study should be considered in planning

future informative quantitative genetic studies, such as modifications of the high-risk paradigm which examine twin similarity for psychopathology in identical and non-identical twin offspring of depressed parents. In addition, there are potential implications for the definitions of the disease phenotype in future molecular genetic strategies which emphasize sib-pair analyses in high-risk families (Risch & Merikangas, 1996), as it appears that anxiety may play an important role as an indicator of familial liability to the affective disorders (Merikangas, 1993).

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