Reviewer's report

Title: Family structure and risk factors of schizophrenia: case-sibling study

Version: Date: 18 June 2004

Reviewer: Angus MacDonald

Reviewer's report:

General

While the liability to schizophrenia is approximately 80% heritable, what causes this inherited liability to manifest as clinical schizophrenia only half the time is an important area of schizophrenia research. Theories as diverse as maternal rearing styles, cat dander, urban living, perinatal complications, and influenza during gestation, and many others, have all had their champions at one time or another. The current study contributes to this literature using data from the large and impressive Finnish national archive to evaluate whether family structure affects the odds of developing schizophrenia. One strength of the study is that this larger cohort enables the authors to model simultaneous a number of correlated family structure variables, such as the number of older sibling, birth order, family size, and maternal age.

Overall, I found the paper easy to read and the operationalization of the measures was neatly spelled-out. Most of my comments pertain to increasing the clarity of the presentation.

-------------------------------------------------------------------------------------------------------------------------

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Methods. For the purposes of this study, sibship was defined as a group of individuals having the same mother. Of course, by this definition some “siblings” may have different fathers and are therefore only half-siblings. While the current database may not be able to disentangle which families include half-siblings, it would be helpful to have an estimate of what proportion may be half-siblings. For example, what is the rate of mothers having children from different fathers during this time period in Finland, or failing that, what is the divorce rate or other information about the stability of families. The authors are encouraged to discuss the implications of allowing heterogeneity of genetic relatedness within families.

-------------------------------------------------------------------------------------------------------------------------

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Results. The nature of the presentation of results does not appear to follow the presentation of the methods or the tables, so it is confusing.

Many readers may not be familiar with the term “primi-“ or “multiparous,” and these may be worth defining for clarity.

References. This citation probably needs editing: Hare EH, Price JS. Birth rank in schizophrenia: with a consider of the bias due to changes in birth rate. British Journal of Psychiatry, 1970;116:409–420.
Discretionary Revisions (which the author can choose to ignore)

Methods. Before removing all single sibship families from the analysis, it would be interesting to test whether single children had the same rate of schizophrenia as first children in multiple sibship families. Of course this would require some estimation of a baserate. Is such a calculation possible through the use of the two databases?

Methods. p.7 The authors state that “...If there were later cases in the family, controls were chosen in the same way but excluding those siblings who already had developed schizophrenia. Thus, a sibling could serve as a control before developing schizophrenia.” For someone unaccustomed to these analyses, this is not at all intuitive. Could the authors include an explanation of why future schizophrenia patients were used as controls, and how the results may have been different if they were simply removed from the analysis (or counted as cases)? Also, on p. 7-8, the authors state “The probands, who were the affected siblings with the lowest age at onset in the families, were not included in this model.” Please elaborate why this procedure did not include the probands. Was this because the family was the unit of analysis?

Methods. Readers would benefit from a more thorough discussion of the difference between conditional and ordinary logistic regression, and more guidance as to which of the analyses are univariate and which multivariate.

In several places in the discussion, there is a tendency to cite literature consistent with the findings without discussing the purported mechanism. For example, on p. 11, the authors allude to early onset as increasing risk for siblings. Why they appropriately cite several familial aggregation studies, there is no discussion of this as an effect of genetic loading which is somewhat curious.

I wish the authors good luck as this project moves forward.

Sincerely,

Angus MacDonald, III, Ph.D.
University of Minnesota
Department of Psychology

**What next?:** Accept after minor essential revisions

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No

**Declaration of competing interests:**

none