Author's response to reviews

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

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Author's response to reviews:

Responses to reviewers report

Reviewer's report
Family structure and risk factors of schizophrenia: case-sibling study Title:
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Angus MacDonald Reviewer:
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.

Authors' response:

We added sentence "Since many of the variables we examined are related to maternal characteristics, we considered it essential that each sibship has the same mother." to the first paragraph of "Methods" section.

The genetists we have been collaborating with in schizophrenia studies have said that in 5-0 per cent of the cases, the father cannot be the one reported by the family.
Since there is this much ambiguity about the identity of the father, we did not consider it essential that the children had the same father in the registers.

We added "Some proportion of siblings of study population are really half-siblings, but even in this case the case-sibling design is applicable, because it do not assume that familial aggregation is due to genetic mechanism." to the "Discussion" section.

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

Authors response: corrected

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.

Authors response: We added "(first delivery)" after the word "primiparous"

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.

Authors response: corrected

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?

Authors response: This would be very interesting, but we consider it to be out of scope of this study. Currently we do not have database for this kind of analyses.

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?


Our study is a matched case-control study where the family was the matching unit. Matching according to family is essential, because siblings resemble each other also due to many others reasons than those included as the explanatory variables. The most important cause for sibling resemblance is
genetic relatedness. The heritability of schizophrenia is approximately 80%, suggesting that the contribution of genetic factors to schizophrenia susceptibility is substantial. Therefore, this matching is essential.

When this so-called case-sibling design is used to study complex diseases with variable age at onset, controls should be sampled from the risk set consisting of those siblings who were disease free at the age the case became affected (the index age). A sibling who is disease-free at the index age but is known to later develop the disease should not be eliminated from consideration as a control, because this would lead to biased estimates.

Case-control studies are used to study the association between disease and one or more risk factors, and this is usually analysed using ordinary logistic regression. However, when the design is a matched case-control study, conditional logistic regression, which takes matching into account, must be used. However, conditional logistic regression could not be used in our study for estimating the effect of variables which had the same value for each sibling of the family, and therefore we used ordinary logistic regression to investigate the effect of these variables. For the variables that were unique for each sibling in the family, results from the conditional logistic regression are more reliable.

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.

Authors response: We corrected table 2 and 3 legends.

We added "Also, a study of parents of patients with childhood- and adult-onset schizophrenia found that parents of patients with childhood-onset schizophrenia had a significantly higher morbid risk of schizophrenia spectrum disorders than parents with adult-onset schizophrenia" \cite{nicolson03:_paren}. All these findings are consistent with the hypothesis that in schizophrenia, as in many other multifactorial neuropsychiatric diseases \cite{kennedy03}, early age at onset is a marker of greater genetic vulnerability to the disorder." to the "Discussion" section.

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

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

Accept after minor essential revisions What next?:
An article whose findings are important to those with closely related research Level of interest: interests
Needs some language corrections before being published Quality of written English: No Statistical review:
Declaration of competing interests:
none

Reviewer's report
Family structure and risk factors of schizophrenia: case-sibling study Title:
This study uses two analytical methods to describe associations between unique and shared family related variables on risk for schizophrenia. The study does address a need, since 1) published data are inconclusive regarding familial risk factors, and 2) the contribution of certain highly correlated family related variables to schizophrenia risk can best be determined using the case sibling design. Many published studies reporting the influence of these factors lacked this design. The study appropriately ascribed the case-sibling design to variables unique to each person and the traditional analyses to a model containing variables shared by more than one person.

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

The manuscript contains numerous spelling and grammatical errors. This is typically not a major issue, but the frequency of such errors in this manuscript warrants serious attention.

The abstract should be more quantitative, providing the most relevant odds ratios and confidence bands.

Authors response: We added quantitative information to abstract and corrected errors.

Results and Discussion sections should be separate.

Authors response: corrected

Page 10: the issue of birth weight among adolescent mothers might explain the observed results; perhaps the authors can provide corroborative data implicating (or not) low birth weight among adolescent mothers as a possible risk factor.

Authors response: Our database do not contain information of birth weights.

Table 2: give the total number of patients with schizophrenia and without schizophrenia, then calculate the percentage of patients with/without the basic characteristic and report these in the table. This provides the reader with information on univariate associations between risk factor and events.

Authors response: columns added to Table 2.

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

Table 3: define/specify the relative estimate (odd ratio?) and level of confidence band (95%?)

Authors response: corrected

Discretionary Revisions (which the author can choose to ignore)

Unable to decide on acceptance or rejection until the authors have responded to the What next?: major compulsory revisions

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

Not suitable for publication unless extensively edited. Quality of written English:

No Statistical review:

Declaration of competing interests:

Employee of a Pharmaceutical company