Author's response to reviews

Title: Psychosis among "healthy" siblings of schizophrenia patients

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Dear Editors,

Thank you for your kind letter (6 October 2005) and the valuable comments by the referees. We found the comments useful, and they helped us to balance the manuscript. Please find enclosed our revised manuscript which we now submit. We have taken account for all the comments and revised the paper...
In the following, the changes we made are described point by point.

I. Referee I (Stephan Arndt) commented that statistical methods were inappropriate because of multiple patients and siblings were from the same families and observations were thus not independent. We reanalysed the data with our statistician Jari Haukka. However, there were numerical convergence problems in modelling, probably due to small cluster sizes and we were able to model only part of the analysis using the general estimation equations method (page 7, last paragraph; see also Results, pages 8-10). However, results were consistent with our earlier findings. We did not reanalyse all the results because t-test is relatively robust against dependence between observations, and differences between siblings and the control group were substantial.

II. Referee I commented that the rule for selecting a sibling was a bit vague. We have rewritten the part concerning the identification of patients and siblings (pages 4-6). In short, the age criterion was set to minimize age- and sex-related differences in neuropsychological performance between affected and unaffected siblings.

III. We now use the term "comparison group" instead of "controls", as referee I suggested.

IV. Referee II (Matti Isohanni) commented that Figure 1 was unclear and that the research process, especially the sampling and formation of the complex study population were poorly described. We have rewritten the part concerning the registers and the identification of probands and their siblings (pages 4-6), and amended Figure 1.

V. Referee II commented that we should describe better the 14 "healthy" siblings who had psychotic symptoms before 1991 and those 16 who developed psychosis from 1991 to 1998. We have added information concerning their diagnosis (Table 1) and rewritten the text (pages 8-9). "Fourteen siblings had had psychotic symptoms before 1991 (see Table 1). "The mean age of onset of psychotic symptoms among 30 siblings according to SCID interview was 33.5, SD 8.7 years. Those 14 siblings who had psychotic symptoms before 1991 had the mean age of onset 26.1, SD 9.4 versus 38.4, SD 5.2 years among those 16 siblings with onset of psychotic symptoms in the follow-up."

VI. On page 9: "Of all 30 siblings with an interview diagnosis of psychotic disorder, seven had had a hospital treatment because of psychotic disorder between 1991 and 1998 according to the Hospital Discharge Register. However, only one of them belonged to the group that had developed psychotic symptoms before 1991."

VII. Referee II mentioned that we should add to discussion the limitations of the generalisation of the results. We have made this on page 13: "Research environment in Finland is unique because of the extensive health care registers, which allow us to identify and follow up patients. However, findings based to register data are not generalizable to countries without such registers.

VIII. Referee II mentioned that we should reread the references 13, 14, 16 and Moilanen et al (2003). We have done this and changed the last sentence on page 4 and added Moilanen et al plus a reference of ours concerning the same isolate. On page 4: " In our own diagnostic reassessment, 69% of the subjects with a register diagnosis of schizophrenia, schizoaffective, or schizophreniform disorder received a diagnosis of schizophrenia, and 87% received any schizophrenia spectrum diagnosis (6). This accords with another validation study from the isolate sample (18), while in the North Finland 1966 Birth Cohort there have been no false positive schizophrenia diagnosis in the Hospital Discharge Register (19, 20)."
IX. Referee II commented that the use of the term "schizophrenia spectrum" was inconsistent. Instead of schizophrenia spectrum psychotic disorders, we have now used the concept of schizophrenia associated psychotic disorders (page 8, Results).

X. Referee II was surprised that schizoaffective disorders were more prevalent than schizophrenia among "healthy" siblings of schizophrenia patients. We have explained: "In 1991, many families already had several members with schizophrenia or schizoaffective disorder. The majority of "healthy" siblings had at that time already passed the greatest risk period for schizophrenia, which explains why only one "healthy" sibling received a diagnosis of schizophrenia during the follow-up. However, there were six with schizoaffective disorder and another six with psychotic affective disorders. In two families the schizoaffective and affective psychotic disorders were clustered with three and four affected siblings in the family. We also found three families with two new cases of psychotic disorders. Our findings accord with several family studies which have reported a high risk not only for schizophrenia and schizoaffective disorders but also for affective disorders within families [1, 2, 3, 30]. Similar findings were seen in a study of extended pedigrees where all patients had a diagnosis of schizophrenia [31]."

XI. Referee II commented that a reference to a textbook (reference1) was questionable. We have added two new references (Chang et al 2002; Austin et al 2005) plus the original reference of Kendler et al.

XII. Referee II commented that we had only one reference in the Discussion on line 16. We have now tried to clarify the sentence and have also given new references. We have also deleted some sentences and partly rewritten the discussion paragraph to answer to question and balance the manuscript.

XIII. Referee II commented that we should comment how the results might be in bias if some psychotic cases were lost due to insufficient diagnostics and powerless registers. We added one sentence on page 11: "The number of false negatives would be high enough to jeopardize the results of genetic analyses, if these siblings were treated as unaffected in the analyses. Even if the "healthy" siblings were treated as unknown, as is the current practise, the analyses would have compromised power compared to more exact diagnoses."

We hope that you will find these changes we have made satisfactory. If requested, we will be happy to modify the manuscript further.

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Thank you for your consideration. We look forward to hearing from you.

Yours sincerely

Dr Ritva Arajarvi