Invited commentaries on:

People at risk of schizophrenia†

TOO EARLY TO PUBLISH RESULTS OF HIGH-RISK SUBJECT RESEARCH

This paper describes the preliminary 'sample characteristics' of the first 100 cases to be recruited to the Edinburgh High-Risk Study of schizophrenia. The senior author has an internationally renowned reputation for work in this area. Unfortunately, this study has some problems as it is currently presented.

The authors do not clarify the aims of this study. The background section is a somewhat muddled and superficial account of neurodevelopmental and genetic theories of the aetiology of the disorder followed by a brief review of previous studies and methods for measuring schizotypy.

The 'Aims' and 'Method' sections (page 548) only address the method. We are not informed how subjects are defined as high-risk until quite late on in the paper. The mixture of two either first- or second-degree relatives leads to a rather variable genetic risk in the subjects, which ranges from approximately 4 to 17% which will make it quite hard to know what results ultimately signify. In other high-risk studies which have looked at the offspring of mothers with schizophrenia, for example, most subjects will have approximately the same genetic risk.

No power calculations are presented. The authors report findings on 100 'high-risk' family members of subjects with schizophrenia and compare these with 30 healthy control subjects. Whether such numbers can generate meaningful results is not clarified. The results suggest that there are very few statistically significant differences and one is inclined to assume that this is because, thus far, insufficient numbers of subjects and controls have been recruited.

It is briefly mentioned in the 'Discussion' that a follow-up will be undertaken in five years. At this time the subjects will be 26.6 (mean) years of age and less than half of those who will subsequently develop the disorder will have had their first hospitalisation (Gottesman, 1994). This would suggest that a 10-year follow-up would be more informative and casts doubts on the hope expressed that using the "period of maximum risk" for these subjects will lead to interpretable results.

These comments apart, the current results are not, in my opinion, of sufficient interest to have warranted publication at this stage. It is unfortunate, especially for more junior investigators, that the results of 'high-risk' subject research may take decades to finalise. It is perhaps understandable that they feel they cannot wait such a length of time to see the fruits of their labour in print.

Gottesman, I. I. (1994) Schizophrenia epigenesis: past, present, and future. *Acta Psychiatrica Scandinavica*, **96** (suppl. 384), 26–33.

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METHODOLOGICAL CONCERNS

The authors introduce us to the Edinburgh High-Risk Study as an attempt to identify individuals at high risk for schizophrenia by using unaffected members of high-density families and a matched 'control' group. Sample size is large, although, this represents only about half of the final sample designed by the investigators. The design is a unique one, to my knowledge. It is likely that this study will contribute substantially to our knowledge about the aetiology of schizophrenia.

Consistent with a number of other studies, the authors found higher levels of a range of so-called schizotypal symptoms and signs in the high-risk *v.* control groups.

A number of methodological issues arise, however. First, it is, in my opinion, incorrect to refer to their control subjects as 'normal'. They could be referred to as 'screened' or 'supernormal', but surely not normal, as these individuals were selected not only for being unaffected, but also for their first-degree relatives being unaffected with any underlying kind of psychiatric disorder including very common ones such as major depression or alcohol dependency. In fact, this is a group that would have substantial selection factors for mental health. I am uneasy with such a selection strategy because it violates the central assumption of epidemiology in that a control group should be identical to your index group in all characteristics except the presence of the index diagnosis. Although not stated, I assume that families of subjects with schizophrenia were not excluded if in addition they had other members with affective illnesses, alcohol dependency, etc. Thus, the investigators are introducing a biased selection which could be responsible for some of the differences observed.

The authors do not describe the actual complexity of their ascertainment of high-risk subjects. In the standard design, in which offspring of affected mothers are followed from a very young age, all high-risk individuals are at approximately equal risks. In the investigators' design, this is absolutely not the case. High-risk subjects can range from having two affected first-degree relatives to no affected first-degree relatives. The former have a higher genetic risk for illness. Furthermore, they are introducing a complex censoring problem by selecting over such a broad age range. Any statistical model of age of onset would suggest that a 25-year-old who remains well is at a considerably lower risk of illness than a 16-year-old who is well. This is because the 25-year-old will have survived a substantial proportion of their age at risk. This is made even more complex because, as realised by Stromgren (1935) earlier in the century, risk is probably also dependent not only on the subject's age, but also on the average age of onset in the family. So an individual who is 25 years old when most members of his or her family have become ill in their late teens in fact has probably survived quite a large proportion of age at risk. By contrast, someone who is 20 years old when the average age of onset in their family runs in the

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late 30s would have traversed almost none of the risk period. Although there are a number of deficiencies outlined by the authors with their high-risk strategy, there are some limitations which they do not outline. The actual risk to illness differs substantially across individual subjects.

To my surprise, the authors never precisely define what they mean by 'well'. In the middle of the 'Results' section, they do make the statement that "no one in either group reached the criteria of a current psychiatric disorder in the PSE or SADS–L". Is that their definition? If someone had a prior episode of psychosis or depression or alcohol dependency from which they recovered and are no longer symptomatic, does that render them well? What about an individual who has four of the nine criteria for schizotypal personality disorder. Would this person be considered 'well'?

The statement on page 547 of the risk for schizophrenia in children of one parent with schizophrenia could hardly be cited in such a definitive way. There is a range of risks and the most recent empirical risk figures from the New York and Copenhagen high-risk studies are different from the summary results presented here. Curiously, they discuss preliminary data supported by Kendler *et al* on the Structured Interview for Schizotypy, but do not cite or comment on complete analysis of the schizotypal symptoms and signs in the Rosscommon Family Study (Kendler *et al*, 1995).

Kendler, K. S., McGuire, M., Gruenberg, A. M., *et al* (1995) Schizotypal symptoms and signs on the Roscommon Family Study: their factor structure and familial relationship with psychotic and affective disorders. *Archives of General Psychiatry*, **52**, 296–303.

Stromgren, E. (1935) Zum Ersatz des Weinbergschen "Abgekurzten Verfahrens". Zugleich ein Beitrag zur Frage von des Erblichkeit des Erkrankungsalters bei der Schizophrenie. *Zeitschrift Gesamte für Neurologie und Psychiatrie*, **153**, 784–797.

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NEED FOR MORE RIGOROUS PRELIMINARY REPORTING

The study describes the design, methods and selected 'baseline' characteristics in a set of 'high-risk' subjects representing 50% of the projected sample size of 100, and in 30 control individuals. The study is prospective by design. The authors also intend to include 30 patients with 'sporadic' schizophrenia. Apart from demographic data, the manuscript includes items from previous history (psychiatric and forensic) and a selection of scores from the Structured Interview for Schizotypy (SIS).

This is a potentially important study which takes a novel approach to the study of risk factors for schizophrenia. However, there is little in this manuscript to justify its publication, since none of the preliminary findings about this half of the sample contributes any new substantive knowledge about the precursors or risk factors in schizophrenia. Hopefully, such knowledge will be forthcoming. The authors should have considered a shorter, tightly written preliminary report outlining more clearly the design of the study and the main background variables describing the study population. Some specific questions that should have been addressed are: (a) Were the SIS interviews conducted blind to the high-risk/control status? (b) How many individuals met the DSM–IV or ICD–10 criteria for schizotypal disorder? A table giving a breakdown of the sample by number of affected family members and degree of relatedness (i.e. affected sibling pairs, parent–sibling, etc.) could have been included as well as a table listing the neuropsychological assessments and the magnetic resonance imaging measures being collected.

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FAMILIES WITH A GENETIC 'TAINT' OR THE TIP OF UBIQUITOUS VARIATION FOR THE HUMAN CAPACITY FOR LANGUAGE?

At first evaluation it seems as though the findings of this study are predictable. Psychiatric illness, forensic contacts and delinquency are higher in the at-risk group than the control group. This could be genetic predisposition or it could presumably be reactive to illness in the family. The increase in premorbid personality anomalies (social isolation, restricted affect etc.) is perhaps more likely to reflect the genetic predisposition. It is consistent with the findings from cohort studies.

The conclusions the authors draw are that the differences may represent increased risk but "their true significance will not be revealed until the cohort has been followed through the at-risk years". An unsympathetic reader might conclude 'let's wait for the full analysis and see – there's no justification for publication at this stage'. Even so, one can ask whether, if the conclusions are relatively predictable at this stage, much more will be achieved with a larger sample and a longer follow-up. Is it not likely that the group who develop a psychotic illness will be more abnormal on these same indices than those who do not? That is, there will be quantitative deviations along the axes of abnormal behaviour and 'schizotypy'.

This question is worth asking because a salient feature of the paper (and maybe the study) is the absence of hypotheses about the nature of the genetic predisposition and the nature of the illness. That there is a category of illness that can be readily isolated and labelled schizophrenia is taken as read (the criteria adopted are not mentioned in the summary), but this is doubtful (see Endicott *et al*, 1982). There are different criteria and there is almost certainly a spectrum or continuum of illness (see Crow, 1994, 1995).

These considerations are no doubt well known to the investigators, but they may be relevant to the way the analysis of the study proceeds in the future. Thus, this background has had no impact on the rather naïve genetic models presented. A further important point (relevant to the issue of the survival of genetic predisposition, considered in the 'Discussion') is uniformity of incidence across populations. As has been argued in the papers cited above, this finding, which has now to be considered relatively securely established, has had no impact on the psychiatric genetic literature or on genetic models. It must mean that predisposition to schizophrenia is a part of variation that crosses the population as a whole. It is the nature of this variation – what are the critical dimensions of variation of which psychosis is the extreme – that is the key question. It seems as though the data in this study, particularly when considered in conjunction with the structural and psychometric studies which, although not mentioned here, are presumably a major part of the

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