

Summary & Critique of Epidemiologic Study

Association between schizophrenia and social inequality at birth: a case-control study

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Description of Study

As the association between social inequality at birth and subsequent risk of schizophrenia is uncertain, this epidemiologic study aims to investigate the relationship between adult-onset schizophrenia and two indicators of social inequality at birth: social class and area of residence. It uses a matched case-control design, which started with 168 first-episode cases of psychosis, identified using a psychosis screen and in-depth assessments. The number of cases is then narrowed down to 82 cases by selecting those born in Nottingham and have information on father's social class (Figure 1). Four age-gender-matched controls were obtained for each of the 94 cases born in Nottingham by selecting the next four births registered at the same birth registry office. Father's occupation and mother's address were extracted from the birth certificates for cases and controls. Father's occupation was then assigned to a social class, and mother's address was used to assign each individual to an area measure of socio-economic deprivation.

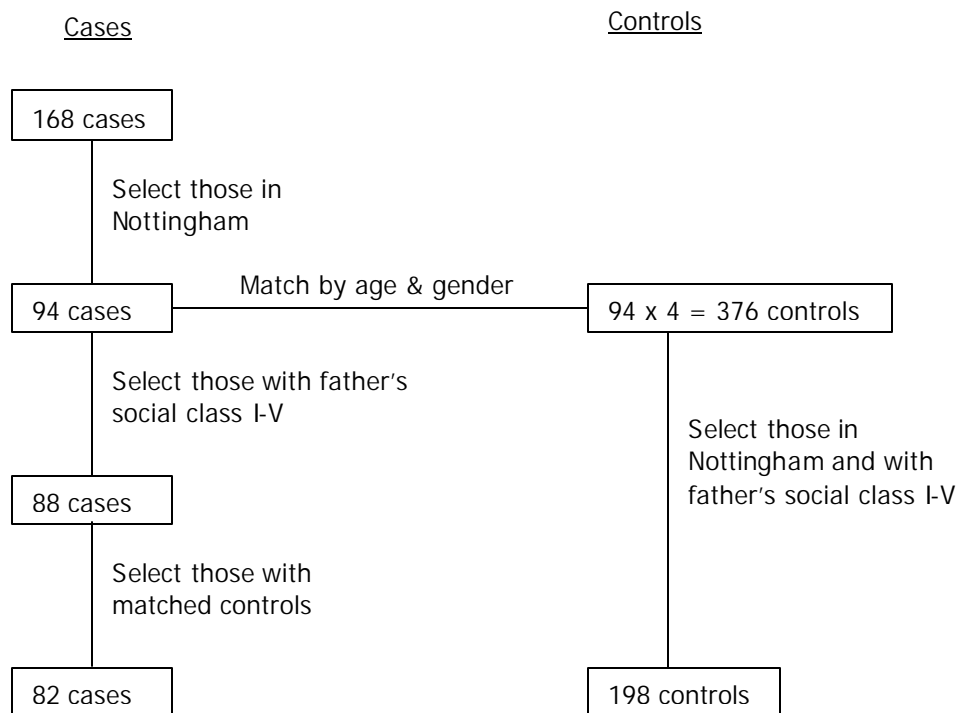


Figure 1: Selection of cases and controls.

Associations of the two indicators were analyzed with all psychotic disorders, followed by a separate analysis for non-affective, non-substance-related psychosis and non-schizophrenic psychosis. Conditional logistic regression analyses and tests for linear trend across social class categories were carried out. To adjust for potential confounding effects, the main analyses were repeated by excluding African-Caribbean cases as well as cases with a family history of schizophrenia. A three-level childhood deprivation score, combining information on place of birth and parental occupation was produced. Appropriate interaction terms were studied to investigate whether associations between childhood socioeconomic deprivation and schizophrenia differed by gender or age.

The results of the study show that risk increased with increasing levels of deprivation at birth. Subjects whose father were social class IV-V or who were born in deprived areas were at increased risk of schizophrenia (odds ratio = 2.1, 95% CI = 0.8-5.5). Risk was greater in those with both of these indicators (odds ratio = 8.1, 95% CI = 2.7-23.9). When broad schizophrenia and other psychoses were examined separately there was evidence that associations are stronger in relation to area of residence for broad schizophrenia. The combined childhood deprivation score showed a highly linear association with all psychoses and for broad schizophrenia, although the association was weaker for non-schizophrenia psychoses. There was no significant interaction between gender and the combined deprivation score with respect to overall risk of psychosis ($p = 0.81$). Weak interactions were found between age and the summary deprivation score with respect to all psychosis ($p = 0.16$) and broad schizophrenia ($p = 0.18$). In a stratified analysis the odds ratio for broad schizophrenia per unit increase in deprivation score was 4.6 (95% CI = 1.9-10.9) for subjects aged > 25 years and 2.1 (95% CI = 1.0-4.2) for subjects aged < 25 years, indicating stronger associations in older subjects. Exclusion of African-Caribbeans or cases with positive family history attenuated the association, suggesting some confounding of the main effects.

The authors concluded that indicators of social inequality at birth are associated with increased risk of adult-onset schizophrenia, suggesting that environmental factors are important determinants of schizophrenic disorders.

Critique of Study

Potential Bias

The hypotheses, methods, results and conclusions are well-summarized at the beginning of the paper, giving a clear overview of the study. In the sample selection, the authors described their selection criteria, appropriately defining 'first-episode' psychosis cases as having a first contact with mental health services for a psychotic illness and highlighting that there was no 'cut-off' point for duration of untreated illness, and any cases with prior episodes of undetected illness were also included. This selection criteria has introduced some selection biases. By using first-episode cases, this method of selection is flawed by uncertainty about the duration of the time period of illness before detection. Case findings were based upon contact with secondary services rather than a systematic community survey. The observed association may have been for risk of making contact with secondary mental health services when developing psychotic symptoms rather than for risk of psychotic illness per se. For this method of selection to be accurate, the lifetime likelihood of schizophrenic patients coming into contact with mental health services must be close to 100%. This percentage, depending on the availability and cost of mental health services, may not sustain because of the growing proportion of patients with schizophrenia treated by general practitioners. The epidemiological validity of this study could be improved if cases that are not in contact with mental health services are also included. Ideally, cases should be entered into the study as soon after onset as possible in order to keep recall deficits, post-onset deaths, and other distorting effects to a minimum.

There was no systematic interview carried out with all first-degree relatives to determine the family history of psychotic disorder, but the study relied upon interviews with patients, case notes and, where available, an interview with an informant. Recall bias could have been introduced as informants may not remember information relating to the patients, and patients too, depending on their mental condition, may not recall the correct or complete information needed for the study. This could have resulted in some underreporting.

There was no attempt made to determine whether controls had schizophrenia. It is assumed that they do not have based on the low population prevalence of schizophrenia. This can result in non-differential misclassification where controls are misclassified as non-cases when in fact they do have the disease. If the controls are misclassified, it would have biased the results toward the null hypothesis.

As information on ethnicity and family history of controls were not available, confounding in these areas could not be explored further, and we cannot ascertain if exchangeability has been achieved. If the ethnicity and family history of controls put them in high-risk, then the study results would reduce the size of any effect and bias the results, again towards the null hypothesis.

There is a potential effect of possibly different migration patterns among cases and potential controls. More affluent cases could have moved out during the prodromal period of psychotic illness, resulting in a biased distribution of social class and area of residence among the remaining cases. This would result in an over-representation of the less-affluent cases and lead to over-reporting.

The authors appropriately highlighted that Nottingham has three birth registry offices, and because both cases and controls would be more likely to register locally, the study may have overmatched for geographical area. This would bias the findings of no difference in area of residence.

Exceptionally high prevalence and incidence rates of schizophrenia in African-Caribbeans have been described since 1967 (Hemsi, 1967). To adjust for possible confounding effects from African-Caribbean family background, stratification is done by repeating the analyses for cases without African-Caribbean ethnicity. The magnitude of the odds ratios was attenuated after exclusion of these cases and their matched controls, suggesting some confounding of the main effects. However, these results have low statistical power due to the small number of cases ($p > 0.05$).

Genetic factors and biological components such as pregnancy and birth complications, as well as prenatal malnutrition, could be possible confounders, and they have not been considered in this study. In addition, the life events of the cases are not studied for confounding factors. Recent studies have reported an excess of stressful life events prior to the onset of psychosis (Bebbington et al, 1993). Stimulants and cannabis can also cause psychotic symptoms (Mathers et al, 1992). These factors are associated with social inequality and onset of psychosis.

Context

A number of causal possibilities, including biological risk factors such as exposure to infections and other toxic agents, and non-biological factors such as social and psychological stressors are linked to the degree of social fragmentation and individual social capital. Causal relationships in schizophrenia are also mediated by complex gene-environment interactions.

This study strengthens the results of some previous studies (Turner & Wagenfield, 1967; Castle et al, 1993) who reported associations with lower paternal social class. However, there are also studies who reported associations with high paternal socio-economic status (Done et al, 1994; Jones et al, 1994; Makikyro et al, 1997), and studies who reported no associations with paternal background (Goldberg & Morrison, 1963). Larger, carefully defined samples are required to clarify these different result findings.

At present many environmental exposures have been examined as possible risk factors, but none has been unequivocally validated and it is possible that different environmental exposures may interact with certain genes at different stages. Rothman's causal heuristic could be used to explain this - an environmental factor may not be a sufficient cause to produce the disease, but it requires genetic factors as a component cause to result in the disease. Environmental factors are found to have varied effects on individuals with different genotypes: Genotypic-environment interactions may result from genetically mediated differences in sensitivity to environmental factors or environmentally mediated influences on gene expression (van Os and Marcelis, 1998).

The odds ratios for association between socio-economic position at birth and adult-onset psychosis have wide confidence intervals. Some of them have confidence intervals ranging from less than 1 to greater than 1, indicating not only a possible weak association, but perhaps no association at all. An example is the odds ratio for broad schizophrenia with paternal social class IV/V – the 95% CI range from 0.6 to 5.8, indicating a possibility that one is less likely to have broad schizophrenia if he has a lower paternal social class (odds ratio < 1).

In the study, social class is determined solely by paternal occupation and area of residence by maternal address. There seems to be an underlying assumption that the father is the only breadwinner of the family and his social class is representative of the family's social status as a whole. The use of maternal address seems to assume that the family unit is intact and thus there is only one area of residence. In the society today, these assumptions are questionable: Firstly, there are generally more working mothers and fathers may not be the sole breadwinner of the family. In a 2002 report by The Institute for Fiscal Studies on mothers' employment in the UK, there are 64% of mothers working. Thus using paternal social class alone may not accurately reflect the social class of the family. Secondly, the family may not be staying together, because the parents are divorced or separated, or due to many possible other reasons. If so, then the question arises on which address to use, and whether maternal address does truly reflect the area of residence of the family.

The results of this study are examined below using Hill's criteria for causation:

- 1) Temporality – The exposure precedes the disease. However, what is questionable here is how the exposure is measured, i.e. the use of father's social class and mother's maternal address to measure the socio-economic position at birth.
- 2) Strength – Though the odds ratios show the strength of the association, the confidence intervals are very wide. The sample size is small, and when breakdowns are done for different psychosis, the p-values obtained are greater than 0.05.

- 3) Dose response - There is a dose-response relationship observed. With lower deprivation score, the odds of adult-onset psychosis increases.
- 4) Replication - As mentioned earlier, different studies have shown differing results so far. Though there are studies that replicate these associations, there are also others that show otherwise.
- 5) Biologic plausibility - It is not specifically addressed in this study.
- 6) Cessation – No, the study is observational and not experimental.
- 7) Specificity – No.
- 8) Consistency - There has been inconsistent results with this association in different studies.
- 9) Alternate explanations - The authors have ruled out some possible explanations in the study. However, as there are other confounding factors not considered, there could be other non-causal reasons for the association observed.

It can be seen that this study meets only some of Hill's criteria. The results need to be investigated further.

Generalizability of the findings

The study excluded cases not born in Nottingham, thus results only apply to people with schizophrenia who continue to reside in a local area after birth and not to all schizophrenic disorders. The small number of cases limited the power of analyses examining relationships with other psychotic disorders ($p > 0.1$).

The biases and confounders explored earlier have undermined the internal validity of this study. To improve the validity, the following could be carried out:

- 1) Increase the sample size, thus increasing the power of the study.
- 2) Redefine case definition to capture those that do not visit mental health services as well.
- 3) Consider other confounding factors.
- 4) Conduct systematic interviews with all first-degree relatives to determine the family history of psychotic disorder for cases.

- 5) Confirm that controls do not have schizophrenia.
- 6) Select controls with ethnicity and family history information.

Originality of the research

This study results add to the accumulating evidence for the role of environmental factors in the etiology of schizophrenia. However, as there are previous studies that did not show the same results, and the presence of potential confounders not taken account into, weakens the results of this study.

Implications

The epidemiological investigation of schizophrenia faces a series of methodological problems at the level of case finding and ascertainment. Firstly, the criteria defining schizophrenia depend critically on the ability to elicit and interpret reports of subjective experience; the prerequisite clinical skills cannot be easily translated into simple tools for case finding in the field. Secondly, there is no biological test or psychometric trait marker of the liability to schizophrenia available for use in population screening. Thirdly, schizophrenia is a low-incidence and low-prevalence disorder and population-based case finding through door-to-door interviewing is costly.

Other methodological problems include the definition of the diagnosis by conventional criteria, the variability of illness courses despite the similarity of psychopathological symptoms, and the heterogeneity of the study populations. The difficulties resulting from non-representative study populations or from a failure to check the findings against alternative interpretations are reflected in the controversy results obtained by different studies as mentioned earlier.

All these methodological problems, if unresolved, will continue to make conclusive interpretations and meaningful comparisons difficult. To date, the extent and nature of environmental contributions to the etiology of schizophrenia still remains elusive.

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