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IQ and risk for schizophrenia: a population-based cohort study

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ABSTRACT

Background. This study aimed to quantify the association between low IQ and the later development of psychosis in a population-based cohort study of 18-year-old conscripts.

Methods. Fifty thousand males conscripted into the Swedish army in 1969–1970 were followed by means of the Swedish National Register of Psychiatric Care up to 1983. Tests of verbal and visuospatial abilities, general and mechanical knowledge and several psychosocial variables were recorded at conscription.

Results. One hundred and ninety-five subjects were admitted to hospital with schizophrenia and 192 with a non-schizophrenic psychosis on ICD-8 criteria. The distribution of scores in those later diagnosed as suffering from schizophrenia was shifted in a downward direction, with a linear relationship between low IQ and risk. This remained after adjustment for potential confounders. The risk for non-schizophrenic disorders was also higher in those with lower IQ but the effect was less marked and non-linear. Only poorer performance on the verbal tasks and mechanical knowledge test conferred a significantly increased risk for schizophrenia after taking into account general intellectual ability. Low IQ at conscription was not related to age of onset.

Conclusions. The results confirm the importance of low intellectual ability as a risk factor for schizophrenia and other psychoses. This is unlikely to be due to prodromal decline or known confounders. The association could be directly causal with cognitive impairment leading to false beliefs and perceptions, or could be indirect with any factors causing lower IQ, such as abnormal brain development increasing the risk for schizophrenia.

INTRODUCTION

An association between low intelligence quotient (IQ) and schizophrenia is apparent from cross-sectional studies that compare current IQ in schizophrenic patients and controls, even when tests are selected on the basis of resistance to change such as the National Adult Reading Test (NART) (Crawford *et al*. 1992). However, such designs cannot exclude the possibility that the disorder itself or its management leads to a decline in IQ (Goldberg *et al*. 1993*a*). (The question of cognitive decline in people with schizophrenia will not be considered further here.) Despite the fact that recent onset cases (Hoff *et al*. 1992), including those who are drug-naïve (Saykin *et al*. 1994), show apparent cognitive impairment, it is necessary to obtain IQ scores prior to the onset of the disorder to establish firmly whether low IQ is a risk factor for schizophrenia. The scores should be obtained safely within the pre-morbid period so as to avoid contamination by any possible prodrome.

Three research methodologies have been applied to these issues, previously reviewed by Aylward and colleagues (Aylward *et al*. 1984).

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Table 1. *Summary of published studies on pre-morbid IQ and schizophrenia*

Study	Schizophrenic cases (*N*)	Pre-schizophrenics' IQ (mean, S.D.)	Controls *N*	Controls' IQ (mean, S.D.)	Difference (95% CI)
Schwartzman & Douglas (1962)	30 (hospitalized)	115·6 (25·1)	1695	127·0 (32·3)	11·4 (−0·23 to 23·0)
	20 (ex-hospital)	117·0 (20·8)			10·0 (−4·2 to 24·2)
Bower & Shellhamer (1960)	44	99·3	44	106·3	7·0
Albee *et al.* (1964)	122 (2nd grade)	93·9 (11·5)	1613	100·8 (10·1)	6·9 (5·02 to 8·78)
	154 (6th grade)	89·4 (15·0)	4166	99·4 (15·7)	10·0 (7·48 to 12·5)
	103 (8th grade)	90·6 (16·2)	4969	99·6 (17·2)	9·0 (12·4 to 15·65)
Offord (1974)	51	88·2 (17·5)	51	100·6 (11·9)	12·4 (16·52 to 18·3)
Watt & Lubensky (1976)	36 (kindergarten)	104·53	36	108·33	3·8
	48 (7–12 yr-old)	102·50	36	107·35	4·85
Griffith *et al.* (1980)	17 (high-risk)	102·3	190 (high risk non-schizophrenic)	100·9	−1·4
			10 (low risk)	104·3	2·0
Erlenmeyer-Kimling *et al.* (1984)	5 (high-risk later hospitalized)	93	80 (high-risk unaffected)	104	11
Ambelas (1992)	18 (child guidance)	87·8	18 (child guidance)	97·1	9·3
Jones *et al.* (1994*a*)	50 (childhood psychiatric contact)	85·4 (17·7)	22 (pre-bipolar)	93·8 (10·3)	8·4 (0·31 to 16·5)
			23 (pre-major) depression)	96·9 (14·4)	11·5 (3·1 to 19·9)
Jones *et al.* (1994*b*)	30	Non-verbal Verbal	4716		Non-verbal Verbal
	at age 8	97·0 (14·1) 96·6 (15·4)			5·9 7·1
	at age 11	96·6 (16·7) 97·3 (15·8)			4·4 5·2
	at age 15	98·9 (15·9) 96·3 (12·5)			9·5 7·5

Standard deviations and values for tests at different time periods given if available. Where results are divided by gender, those for males are included.

Case–control studies using school or clinic assessments of IQ

A number of the early US studies are of doubtful relevance because of the wide concept of schizophrenia employed in the US at that time (Kendell *et al.* 1971). Nevertheless, these studies appeared to demonstrate an association between low IQ and a diagnosis of schizophrenia, as defined at that time. Such studies were reviewed Aylward *et al.* and are summarized in Table 1 along with more recent work.

Using child guidance clinic (CGC) records, Ambelas (1992) traced 18 schizophrenic cases born between 1954 and 1961 in an English district, and matched them with the next CGC attender referred for the same reasons. The distribution of IQ was shifted in a downward direction. Finally, Jones and colleagues (1994*a*) from the Maudsley Hospital traced the records of those adult psychiatric patients who had childhood psychiatric contact with the same hospital. Differences were seen between schizophrenics- and affectives-to-be.

Case–control studies are susceptible to selection bias and one methodological concern about some of these studies is that cases and controls came from different populations. A proportion of members of the school population may leave the area before or after graduating from high school and would, therefore, no longer be at risk of becoming a case in the study. It is difficult to assess the size of this bias so these studies must be interpreted cautiously. Not all studies used incident cases so that the association with low IQ may have been confounded by chronicity and severity.

High risk studies

Children of schizophrenic mothers have also been used to address the question of whether there are significant and identifiable cognitive and intellectual impairments prior to the development of schizophrenia. Unfortunately, studies have rarely involved sufficient numbers of schizophrenic subjects – either because of the small sample of children originally recruited or because follow-up has yet to pass through the age of risk – to add meaningfully to this issue. The largest of these (the Copenhagen High Risk Study) (Griffith *et al.* 1980) failed to find significant differences (1·4 IQ points; 95% CI −6·1 to 8·9 assuming a standard deviation of 15) between children of schizophrenic mothers

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who did or did not develop the disorder at follow-up using the Wechsler Intelligence Scale for Children (WISC). The New York High Risk Study (Erlenmeyer-Kimling & Cornblatt, 1984) produced data on a handful of cases who developed schizophrenia (included in Table 1 for completeness). Studies of siblings and children of schizophrenics showing varying degrees of cognitive impairment are not relevant in that we are concerned here with only those cases who develop the full-blown disorder.

Population-based studies of IQ and schizophrenia

Army cohorts have been exploited usefully in the study of risk factors for the development of psychosis for several decades (see Mason, 1956; Schwartzman & Douglas, 1962; shown in Table 1). While such studies are valuable, they did not adjust for person-years at risk, neither was account taken of changes in IQ over time in the population and the diagnoses of schizophrenia would probably not correspond to modern criteria. Nevertheless, they all point to premorbidly lower than average IQ in those who developed the disorder.

More recently data have been published on two British National birth cohorts. The first of these is the National Survey of Health and Development (Jones *et al.* 1994*b*). A random sample of all births in a single week in March 1946 (approximately 5000) was studied on 19 occasions between the ages of 2 and 43 years on a number of health and social variables. Cases of schizophrenia were identified in the course of these assessments and from an administrative central register of psychiatric hospital admissions in Britain – the Mental Health Enquiry (MHE) (active between 1974 and 1986).Thirty cases were identified as meeting DSM-III-R criteria for schizophrenia. The cases tended to score lower on all tests of educational abilities carried out at ages 8, 11 and 15, the deficit increasing with age. When scores were normalized on a sample mean of 100, there was a deficit ranging from 3·1 points for vocabulary (21% of an S.D., NS) to 9·5 (63% of an S.D.) for a non-verbal test, $P = 0{\cdot}002$. A linear trend was found in the association between low IQ and schizophrenia with a rate ratio of 4·0 between the lowest and highest tertiles.

The other cohort was started in 1958 and became known as the National Child Development Survey (Done *et al.* 1994). It too consisted of all births in a single week. Individuals were assessed at ages 7, 11 and 16 on a large variety of health, psychological and social variables. Cases of schizophrenia were again retrieved from the MHE and diagnoses checked against the PSE-CATEGO system (Wing *et al.* 1974). There were approximately 40 such cases who met 'narrow' criteria and these were contrasted with a comparable group of pre-affective disorder and pre-neurosis children. The pre-schizophrenics showed a stable pattern of psychometric test score deficits of around 8–9 IQ points, i.e. 0·6–0·7 of an S.D. (John Done, personal communication).

Specificity: deficits and diagnoses

The data summarized in Table 1 point to premorbid IQ being substantially lower in those children and adolescents who go on to develop schizophrenia. This raises a subsidiary question as to whether any dimension of intelligence is particularly related to the later development of schizophrenia such as visuospatial as opposed to verbal IQ. One fairly robust finding in the neuropsychology literature is that patients with schizophrenia tend to have higher verbal than performance IQ (Aylward *et al.* 1984). More recent reviews (Cutting, 1990) confirm this pattern which appears to be specific for schizophrenia (Cuilari, 1985). The only prospective studies able to address this question adequately are the British cohort studies. Jones *et al.* (1994*b*) had five test categories: non-verbal, verbal, arithmetic/mathematics, vocabulary and reading. Curiously, only the first three of these showed significant differences between cases and controls, that is 'verbal' tests but not reading and vocabulary. However, the authors did not adjust for the intercorrelation of the scales and may not have had the statistical power to do so.

The problem of confounding must be addressed in studies of IQ and psychiatric disorder. Clearly an apparent association between low IQ and schizophrenia may arise because of the deprived sociocultural *milieu* in which psychiatric disorders arise (although social class was not a confounder in the British cohort studies) or because psychiatric disturbance in other family members may increase the genetic risk for a disorder in a proband as well as interfere with

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his or her educational attainment (i.e. shared non-genetic factors). Studies which have compared schizophrenic-to-be children with their siblings, have confirmed patients' lower premorbid IQ but reveal a less marked discrepancy than when classmates are used for comparison. The greatest discrepancy arises when schizophrenic-to-be children are compared with population norms (Aylward *et al.* 1984).

Regarding specificity, there are some prospective data relating IQ to psychiatric disorders other than schizophrenia although one study hinted at possibly higher IQ in future manic depressives (Mason, 1956). Many high risk studies have shown some reduction in IQ in the offspring of other psychiatric patients, usually somewhat less marked than in children of schizophrenics (Asarnow, 1988). Done *et al.* (1994) found that future neurotic and affective disorder individuals showed a reduced IQ, midway between normals and pre-schizophrenics (Done, personal communication). These cohort studies have limited power to examine the pattern and specificity of data given the number of cases of schizophrenia involved.

The current study

We report on an entire population of nearly 50000 18-year-olds from a Swedish conscript cohort who underwent extensive cognitive testing, and who were followed up until age 33–34 years through a National Case Register which recorded psychiatric diagnoses on admission to hospital. This is larger than the previously published studies and as well as investigating the general question of whether low IQ is associated with the later development of schizophrenia, we will also consider: whether specific patterns of impairment, for example visuospatial or verbal are related to schizophrenia; whether low IQ is associated with non-schizophrenic psychoses; the extent to which IQ may be confounded by other social and psychological parameters; and, whether low IQ is associated with an earlier age of onset (Offord & Cross, 1971).

METHOD

Subjects

A total of 49968 18-year-old males conscripted into the Swedish army during 1969–1970 on whom IQ scores were available formed a cohort for the current study. Previous research based on Swedish conscripts (Lewis *et al.* 1992), has used a slightly different but overlapping group which included individuals who, for various medical and social reasons, entered the army later at age 19 or 20 years. Only 2–3% of the male population were excused conscription on account of severe mental or physical handicap. The conscription procedure takes $1\frac{1}{2}$ days for each subject and consists of a series of tests of physical and mental health status, personality and intellectual capacity. A full medical examination is carried out and if any disease or disability is reported or discovered, a more thorough examination is performed. Each subject answers self-administered questionnaires on family, social background, and behaviour during adolescence. All are given a structured interview by a psychologist and those reporting any psychiatric symptoms or current problem under treatment, are interviewed by a psychiatrist and, in this cohort, given a diagnosis according to ICD-8 (World Health Organization, 1974) where applicable. The whole procedure is aimed at detecting disease as well as identifying persons suitable for higher military training, hence the threshold for referral to the psychiatrist was low. Thirty-three cases of psychosis were diagnosed at the time of conscription and these were excluded from the cohort since the conscription assessments were not prospective with respect to the disorder. Other non-psychotic psychiatric diagnoses were noted and treated as potential confounders in the analyses. Permission to use the data base for research was granted by Research Ethics Committee of the Karolinska Institute and the Swedish Data Inspection Board.

Intellectual and cognitive tests

There were four main subtests which each yielded a 9-point summary score. These were aggregated to give an overall intelligence score. All tests were progressive, beginning with relatively simple questions and becoming more difficult.

The subtests

The verbal IQ test, lasted 7 min and consisted of 40 questions. Subjects were given rows of five words and told to underline the odd one out e.g. '<u>teapot</u>, sandwich, milk, egg, meat.',

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and more difficult, 'insist, request, question, believe, admire'.

Visuospatial tests took 40 min and took the form of a probe geometric shape (e.g. an isosceles triangle bisected by a vertical line) followed by four items consisting of different pairs of triangles of different sizes and in different orientations. Subjects were asked to state which of the choices could make up the probe item.

A general knowledge and intelligence test consisted of 40 items and took 12 min. Subjects would be presented with an array of shapes and letters in combination and the question would run as follows: 'Put a line through the square under the longest word,' (out of 5). More difficult: 'Fill the square furthest up to the right and the second square from the left in the lowest row. After that fill in each 4th square from the left in the second row from the bottom and every other square from the right in the second row from the top,' (presentation of a grid of small squares). Also included were miscellaneous and general knowledge questions e.g. 'Where is Sweden in relation to Denmark'; 'if a clock shows 10 minutes past 12 what would be the time if the hands changed places?'; simple arithmetic (adding and/or subtracting two numbers), and more complex calculations, e.g. 'underline the number which multiplied by itself and divided by 2 gives a number which is twice as big as the second from last number in the row'. The entire test clearly taps many integrative cognitive functions.

The fourth subtest comprised diagrams representing complex problems requiring mechanical ability and a knowledge of basic physics. For example, a 100 kg bail of hay and 100 kg of sand both resting on a sharp incline. The question was which would tip over more easily? Another example was of a penny-farthing bicycle with the question, which wheel goes round the most times in 100 metres? Other questions were based on weights and levers, projectiles and trajectories, simple electricity, momentum, etc. Again, it is not clear precisely what this battery tests but reasoning about the behaviour of objects in the real world seems to be involved in most tasks, some of it knowledge-free and some, requiring acquaintance with the laws of physics.

Scores on these tests had been standardized against an entire conscript cohort from a previous year and were placed in nine bands. The nine bands corresponded to: 4%, 7%, 12%, 17%, 20%, 17%, 12%, 7%, 4% of the distribution. Given that IQ is a standardized measure with a normal distribution and mean set at 100 and S.D. of 15, it is possible to estimate, using published tables of the normal distribution, the approximate IQ band for each of these nine categories. These are given in Tables 2 and 3.

Follow-up

The Swedish National Register of Psychiatric Care recorded about 70% of all admissions in 1970 rising to 83% in 1973. From 1974 to the end of 1983 the coverage was between 97 and 98%. The register was closed in 1983. The register also provided a date for the first admission to psychiatric hospital after 1973.

Psychiatric diagnosis

The patients were given clinical diagnoses according to the Nordic version of ICD-8 (World Health Organization, 1974). The two end-points analysed were admission for schizophrenia (codes 295.00 to 295.99) and other psychoses (codes 296.00–299.99), as well as year of entry onto the case register (year of first admission). Diagnoses have been found to have approximately 85% specificity and sensitivity when measured against DSM-III (Kristjansson *et al.* 1986). In addition, a random selection of cases from the National Register was recently retrieved and diagnoses checked. A validity study on cases treated within the Stockholm county area, has confirmed these results on 40 schizophrenics whose records were retrieved, in which 29 met DSM-III-R schizophrenia criteria (plus four who were schizophreniform), equivalent to 82% specificity. In addition, of 30 non-schizophrenic psychotics, only four met criteria for schizophrenia or schizophreniform disorder (87% sensitivity), the rest were correct.

Statistical analysis

Odds ratios and 95% confidence intervals (CI) were calculated with logistic regression using the program Stata (*Statistics Data Analysis*, 1994). Adjustment for potential confounders was performed by adding variables to logistic regression model containing the IQ variable. Logistic regression models were compared using like-

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Table 2. *Odds ratios* (95% *CI*) *for schizophrenia by the nine overall IQ bands*

IQ	< 74	74–81	82–89	90–95	96–104	105–110	111–118	119–126	> 126
Non-cases	1963	2644	4852	7080	8628	8855	7427	5098	3226
Schizophrenia cases	26	17	27	38	25	24	23	10	5
% in each IQ category	3·9	5·3	9·8	14·2	17·3	17·8	14·9	10·2	6·5
Odds ratios (95% CI)	8·6 (3·1–25·4)	4·2 (1·4–12·9)	3·6 (1·3–10·6)	3·5 (1·3–10·0)	1·9 (0·7–5·6)	1·8 (0·6–5·2)	2·0 (0·7–6·0)	1·3 (0·4–4·2)	1·0*
Positive predictive value (%)	1·3	0·6	0·6	0·6	0·3	0·3	0·3	0·2	—

* Baseline.

Table 3. *Odds ratios* (95% *CI*) *for other psychoses by the nine overall IQ bands*

IQ	< 74	74–81	82–89	90–95	96–104	105–110	111–118	119–126	> 126
Non-cases	1956	2649	4858	7101	8624	8844	7427	5096	3221
Cases	33	12	21	17	29	35	23	12	10
% in each IQ category	3·9	5·3	9·7	14·2	17·2	17·7	14·8	10·2	6·6
Odds ratios (95% CI)	5·4 (2·6–11·8)	1·5 (0·6–3·6)	1·4 (0·6–3·2)	0·8 (0·3–1·8)	1·1 (0·5–2·4)	1·3 (0·6–2·7)	1·0 (0·5–2·2)	0·8 (0·3–1·9)	1·0*

* Baseline.

lihood ratio tests. This was done when comparing models containing linear terms for IQ with those in which the nine IQ categories were represented by separate dummy variables. Likelihood ratio tests were also used to test for statistical significance when the four IQ subscales were investigated. The tests compared models containing all four subscales with the three remaining variables. For some analyses the effects of IQ were modelled as a continuous variable, so the odds ratios reported are those for an increase of 1 in the 9 point scale.

RESULTS

The effect of IQ and later psychotic illness is highly significant for both the 195 schizophrenics ($\chi^2 = 70{\cdot}8$, df = 8; $P < 0{\cdot}0001$) and the other 192 psychotics ($\chi^2 = 94{\cdot}1$, df = 8; $P < 0{\cdot}0001$) admitted during the follow-up period. Table 2 shows the odds ratios for schizophrenia for subjects scoring in each overall IQ band. The proportion of the remaining population in each band shows the approximately normal distribution of scores although there appears to be a slight overall improvement in scores compared to the reference population. The positive predictive value for low IQ is poor with below average IQ (< 96) predicting only 3·1% of cases.

The odds ratios in Table 2 suggests a non-linear relationship between IQ and schizophrenia risk, with those in the lowest band having a greater risk than one would expect from a linear relationship. However, there was no statistically significant departure from a linear relationship for schizophrenia ($\chi^2 = 7{\cdot}2$, df = 7; $P = 0{\cdot}41$), although there was a significant deviation in the other psychosis group ($\chi^2 = 31{\cdot}8$, df = 7, $P < 0{\cdot}0001$) (Table 3). Subjects scoring below the 96–104 or middle band were at significantly increased risk of schizophrenia. This effect was much weaker in the other psychotic group, with odds ratios remaining below 2 for all performances scoring better than the lowest (IQ < 74) band. The possibility that a quadratic term would improve the fit between IQ score and the risk of developing schizophrenia and other psychoses was also examined. There was no evidence for this in schizophrenia ($\chi^2 = 1{\cdot}79$, df = 1; $P = 0{\cdot}18$; odds ratio 1·02, 95% CI 0·99–1·05). For the other psychoses however, there was a statistically significant quadratic term between IQ score and other psychoses ($\chi^2 = 15{\cdot}2$, df = 1; $P < 0{\cdot}0001$; odds ratio 1·05, 95% CI 1·02–1·08).

IQ subtests

The four subscales intercorrelated (Table 4); the highest correlation was between verbal and visuospatial scales $r = 0{\cdot}75$; i.e., about 50% of the variance was common to these two measures. This would not be expected to affect the logistic regression model in which all four subscales were entered (overall IQ was not included). The stability of the estimates was tested by removing variables from the model including all four subscales. This confirmed that the verbal and mechanical knowledge subtests were those that were independently associated with schizophrenia while the visuospatial scale provided least discrimination between the three subject groups. Only verbal IQ was related to 'other psychoses' (see Tables 5a and b).

Fig. 1 displays the proportions of pre-schizophrenics, pre-non-schizophrenic psychotics, and non-psychotic controls who scored in each of the nine IQ bands on the mechanical knowledge tests. There is a left-shift in the distribution of the patient groups' scores, most obvious in the pre-schizophrenic group. The curves for both patient groups remain below the normals' curve at IQs above 104, and tend to rise above it at IQs below 96 for all of the four subtests (data not shown). An exception to this is in the verbal IQ test in which 20·3% of the non-schizophrenic psychotics were in the 105–110 band compared with 16·8% of normals and 10·8% of pre-schizophrenics.

Table 4. *Correlations between the four subscales and overall IQ score*

Test	General knowledge	Verbal	Visuospatial	Mechanical knowledge
General knowledge	1·0			
Verbal	0·748	1·0		
Visuospatial	0·520	0·507	1·0	
Mechanical knowledge	0·586	0·545	0·499	1·0
Overall IQ	0·863	0·847	0·750	0·751

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Table 5. *Relationship between measures of IQ and (a) schizophrenia and (b) other psychoses before and after adjusting for inter-correlation between subscales*

Measure	Odds ratios (95% CI)		χ^2	P
	Before adjustment	After adjustment		
(a) Schizophrenia				
Overall IQ score	1·27 (1·19–1·36)			
Subscales				
General knowledge	1·22 (1·13–1·31)	0·97 (0·86–1·09)	0·3	0·58
Verbal IQ	1·26 (1·17–1·35)	1·12 (1·00–1·26)	3·6	0·06
Visuospatial IQ	1·19 (1·11–1·29)	1·00 (0·91–1·10)	0·01	0·96
Mechanical knowledge	1·36 (1·26–1·47)	1·30 (1·17–1·44)	25·9	< 0·001
(b) Other psychoses				
Overall score	1·19 (1·11–1·28)			
Subscales				
General knowledge	1·15 (1·07–1·24)	0·95 (0·94–1·19)	0·8	0·36
Verbal IQ	1·20 (1·12–1·29)	1·15 (1·02–1·29)	5·54	0·02
Visuospatial IQ	1·19 (1·11–1·29)	1·08 (0·98–1·19)	2·54	0·1
Mechanical knowledge	1·18 (1·10–1·28)	1·09 (0·99–1·20)	2·9	0·09

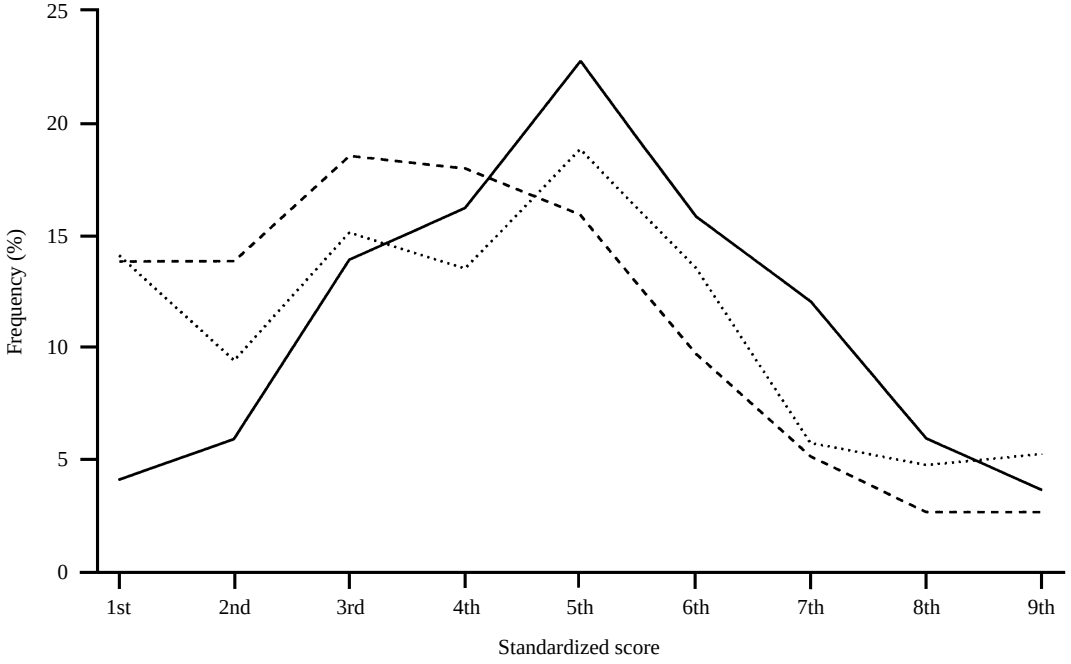


FIG. 1. Frequency (%) of pre-schizophrenic (– – – –) ($N = 195$) and pre-non-schizophrenic psychotic (· · · ·) cases ($N = 192$) plus normal population of 18-year-old male Swedish conscripts (——) ($N = 49850$) in each of nine standardized IQ bands on tests of 'mechanical knowledge'.

Adjustment for confounders

The association between IQ and schizophrenia was re-examined after adjustment for the following potential confounders: family finances (socio-economic status), behavioural and school adjustment, drug abuse, urban upbringing, family history of psychiatric disorder and psychiatric disturbance at the time of testing. The effect of low IQ was still highly significant (odds ratio 1·28; 95% CI 1·18–1·38) for schizophrenia, for each IQ band. The association between IQ and other psychoses was also significant (odds ratio 1·22; 95% CI 1·13–1·32). Note that

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Table 6. *Relationship between IQ and schizophrenia by year of first admission*

Year of first admission	Cases *N*	Odds ratios (95% CI) for schizophrenia, after adjustment*
1973–4	90	1·21 (1·09–1·36)
1975–8	75	1·26 (1·12–1·42)
1979–83	30	1·45 (1·19–1·76)

* Adjusted for diagnosis at conscription, place of upbringing, family finances, behavioural and school adjustment, drug abuse and family history of psychiatric disorder.

although non-psychotic disorders were associated with low IQ at conscription, behavioural variables such as sensitivity and preference for socializing in small groups were generally associated with high IQ (Malmberg *et al.* 1997).

Age at onset

Finally, the effect of pre-morbid IQ and year of first admission was considered (Table 6). The association between schizophrenia and low IQ was present in all three time periods. Even in those first admitted after 1978, 8 or 9 years after the original measurement of IQ score, still showed a statistically significant association with IQ, after adjustment for the potential confounding variables.

DISCUSSION

We report a highly significant association between low IQ scores in young men, tested at 18, and the subsequent development of schizophrenia. There was a linear relationship between schizophrenia and IQ, with risk gradually increasing as IQ falls at all levels of intellectual ability. This argues against the notion that there is a small subgroup of individuals at risk, that can be identified by their low IQ. Risk of schizophrenia is a continuous function of IQ over the whole range of IQ scores in the population.

Individuals with a major neurological or learning disability and those who had developed schizophrenia by age 18 were excluded from this cohort. It is possible that this may have biased the sample away from very severe 'neurodevelopmental' cases of schizophrenia and hence to an underestimate of the association between low IQ and the disorder. On the other hand, cases with an age of onset after 34 years and some cases with a single episode during the earliest phases of the Swedish National Register (i.e. better prognosis cases) would also have been missed. Despite these reservations we are confident that the results are generalizable to the vast majority of male cases of schizophrenia. Female cases are well known to have a slightly later age of onset and some authors have argued that they show less cognitive impairments (Aylward *et al.* 1984; Castle & Murray, 1991) although empirical support for this is lacking (see Jones *et al.* 1994*b*; Goldberg *et al.* 1995).

The follow-up using the case register began in 1973, 3 to 4 years after the initial survey. However, we would expect most early onset cases to relapse within the succeeding 10 years and so be included in the register. During the period of follow-up there were some movements towards increased community care in Sweden, but it is likely that the vast majority of people with schizophrenia would have been admitted to a psychiatric hospital.

The IQ scores here were calculated from four subscales. Though the IQ scales were not part of an internationally recognised psychometric battery, they were administered carefully, in a standardized fashion, and this sample itself provides good normative data for the population. Two of the scales are easy to identify as requiring verbal and non-verbal skills. The other two are best described as assessing 'general knowledge' and 'mechanical knowledge'. It appeared 'mechanical knowledge' (and to a lesser extent, verbal IQ) was independently associated with schizophrenia after adjusting for the other three subscales. Psychological research in schizophrenia is replete with attempts to discover a differential deficit (Chapman & Chapman, 1973), that is, a disproportionate impairment in one test or faculty, against a background of (usually) global impairment, few of which have been successful (Blanchard & Neale, 1994). The study of IQ in relation to schizophrenia on the other hand, presupposes that some general ability is deficient and the data summarized in Table 1 support this view. Our findings suggest that this global impairment is a powerful predictor of later schizophrenia but that deficits in specific cognitive skills, may confer an additional risk. A cross-sectional study (Crawford *et al.* 1993) of patients with schizophrenia in which poor verbal fluency perform-

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ance was associated with the diagnosis after adjusting for IQ, is consistent with this. Mechanical knowledge, like verbal fluency could be conceived of as a task requiring executive control which in turn may be reliant on frontal lobe functioning, often implicated in neuropsychological studies of schizophrenia (Goldberg & Weinberger, 1992). Verbal IQ as estimated in this study appeared to be highly dependent on verbal memory and word meaning, a component of semantic memory, specific impairment of which has also been claimed in schizophrenia (Tamlyn *et al*. 1992; Saykin *et al*. 1994).

We were also able to compare the results for schizophrenia with those for non-schizophrenic psychoses. The association was in the same direction but less strong, consistent with studies on patient groups (Goldberg *et al*. 1993*b*). Unlike the situation with schizophrenia, there was also some evidence that those in the lowest IQ band were at especially increased risk of other psychotic illness, over and above the risk expected from a linear relationship with IQ. These results, therefore, suggest that other factors are more important in the development of non-schizophrenic psychosis in those of average or above average IQ, in contrast to the clearer dose-response relationship observed for schizophrenia (Hill, 1965), and hence points to aetiological heterogeneity.

Explanations

How then do we explain the results and what are the implications for theories of schizophrenia?

1 Prodrome

It might be argued that the low IQ scores merely reflect low functioning resulting from a prodrome to the illness. We believe this is unlikely as the association with IQ was still apparent even in those first admitted up to 10 years after the initial interview, and in fact tended to be stronger in such cases compared to those with earlier onset. Furthermore, our results are consistent with others (Jones *et al*. 1994*b*) who found an association between low IQ in 8-year-olds and the later development of schizophrenia.

2 Confounding

The association between low IQ and schizophrenia could be confounded by a third factor(s)

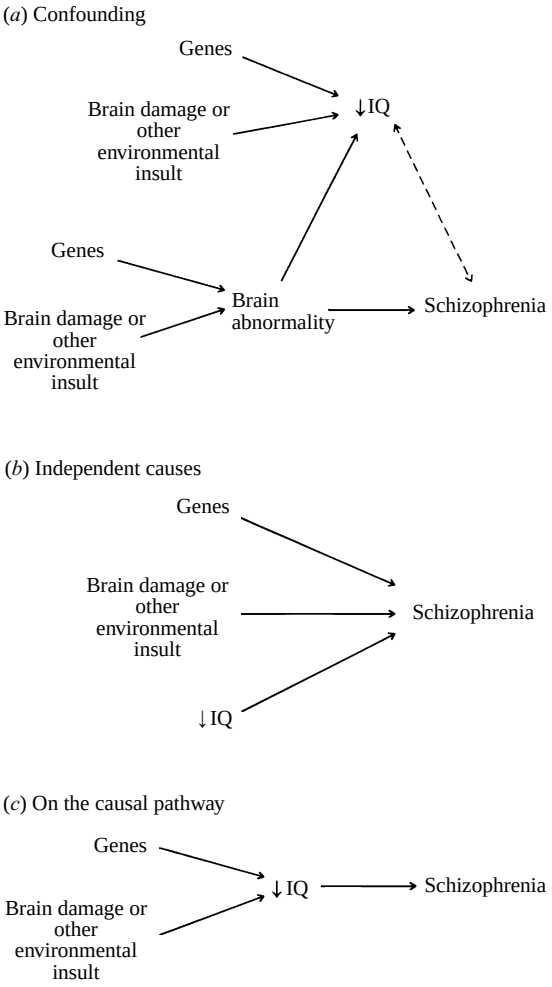


FIG. 2. Diagrams illustrating: (*a*) confounding in the association between low IQ and the development of schizophrenia; (*b*) independent causes, including low IQ, associated with the development of schizophrenia; and (*c*) causes of schizophrenia with low IQ on the causal path.

producing both low IQ and schizophrenia independently (Fig. 2*a*). In the analysis we have adjusted for a number of confounders including social and behavioural difficulties (such as having few friends or intimate relationships), that we have identified in this cohort (Malmberg *et al*. 1997); family finances, place of upbringing and psychiatric diagnosis at conscription (Lewis *et al*. 1992). However, there may be other potential confounders, known or unknown, which were not taken into account.

One of the main themes in recent thinking

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about the aetiology of schizophrenia is the so-called neurodevelopmental hypothesis, that schizophrenia arises from early possibly foetal abnormalities of either genetic or environmental origin (Jones & Murray, 1991). Our analysis attempted to adjust for genetic effects by using family history, assessed rather liberally by the presence of a family member on psychotropic medication, and this did not affect the results. Data from monozygotic twins discordant for schizophrenia also address this issue. Goldberg *et al.* (1990) showed that the schizophrenic twin was invariably intellectually impaired compared to his/her co-twin. That is, when genetic risk is controlled, the independent association with IQ remains, though it is also possible that genetic influences on schizophrenia could be mediated by genetic influences on IQ (Cannon *et al.* 1994). However, it is difficult to explain the association between low IQ and schizophrenia if it is due to environmental factors, using known risk factors for schizophrenia. For example, obstetric complications, confer an approximately two-fold risk of schizophrenia only (Geddes & Lawrie, 1995) and so are unlikely to entirely account for the strength of association found here.

3 Causality

We believe that low IQ can be considered as a possible causal risk factor for psychosis, as it is in childhood psychiatric disorders (Goodman *et al.* 1995) and Alzheimer's disease (Ott *et al.* 1995). As stated above, other known environmental risk factors, seem to be unable to account for an association of this size. While there is always the possibility that unknown confounders could cause this association, a strong statement of our hypothesis is that low IQ itself increases the risk of later developing schizophrenia (Fig. 2*b*). Since the positive predictive value of low IQ is so poor, other risk factors must also be involved. Most if not all putative risk factors for schizophrenia show a relationship with lower IQ, obstetric and birth complications being prime examples (Aylward *et al.* 1989; Buka *et al.* 1993). Hence, our third model is that lowered IQ could be the means by which other genetic or environmental influences increase the risk of schizophrenia (on the causal path (Erlenmeyer-Kimling *et al.* 1991)) (Fig. 2*c*). Of course, all the options shown in Fig. 2*a–c* could be operating simultaneously.

Possible mechanisms

A psychological explanation could be advanced whereby the lower a person's IQ the less likely s/he is to comprehend the complexities of society and social interaction and this could lead to misunderstandings, feelings of paranoia and social withdrawal. Deficits in social cognition are well recognized in patients with schizophrenia and appear to be stable and unrelated to other aspects of psychopathology, in contrast to the non-schizophrenic psychoses (Bellack *et al.* 1994).

In a more general sense, low IQ could compromise information processing leading eventually to the psychopathology of schizophrenia (David & Cutting, 1994). A number of conditions which reduce cognitive functioning also appear to be associated with an increased risk of psychotic symptoms (delusions and hallucinations), for example, Huntington's disease and Alzheimer's disease, head injury, epilepsy, etc. (Davison & Bagley, 1969). Similarly, people with learning disability (mental handicap) from various causes are at significantly increased risk of psychosis (Hallgren & Sjögren, 1959; Reid, 1989). Looking at this another way, it could be stated that high IQ is protective against schizophrenia. High IQ is associated with preserved insight in psychosis (David *et al.* 1995) and may prevent the sort of 'jumping to conclusions' thought to underlie delusions (Garety, 1991). This would predict that any of the above acquired disorders would be less likely to lead to schizophrenia in a person of high IQ. Furthermore, any factors that cause reversible schizophrenia-like psychoses, such as chronic amphetamine abuse (Connell, 1958) should be less psychotogenic in people with higher IQs (and vice versa). These hypotheses are eminently testable.

In theory, if low IQ is a risk factor for schizophrenia and not merely a confounder or an epiphenomenon of a neurodevelopmental insult, improvement of IQ should reduce the risk of schizophrenia. This implies some potential for prevention. It is unlikely that this theory could ever be tested directly given the size of cohort one would require.

Future research that identifies potential risk factors for schizophrenia will help to unravel this issue by determining whether the strong

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association between IQ and schizophrenia results from confounding. Obviously, identification of genes that increase the risk of schizophrenia would also help to clarify this relationship. Such genes may act by lowering IQ.

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