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Population-based Cohort Studies on Premorbid Cognitive Function in Schizophrenia

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Many previous studies have found associations between poor cognitive function and schizophrenia. However, the majority of these studies used retrospective data, leading to the possibility of selection and recall biases. Retrospective studies are also unable to distinguish whether cognitive deficits exist prior to the onset of schizophrenia, suggesting that they are important in etiology, or following onset, suggesting that they are secondary to the disorder or its treatment. The current review used a systematic search strategy to identify and summarize the results of all studies that have used population-based cohorts to examine associations between prospectively collected data on premorbid cognitive functioning in childhood or adolescence and subsequent risk for schizophrenia. Three broad categories of study have addressed these questions: birth cohort designs with cognitive testing during childhood, army conscript designs with cognitive performance measured at conscription, and studies using school grades. Birth cohort and conscript studies are consistent in reporting strong associations between poor performance on cognitive batteries and increased risk of schizophrenia. Studies on school performance have been less consistent, although the largest such study showed strong associations across all school subjects. In conclusion, children and adolescents with poor cognitive abilities in childhood are at increased risk of schizophrenia. This suggests that poor cognitive function is either directly causal or associated with causal factors that are involved in etiology.

adolescent development; child development; cohort studies; intelligence; learning disorders; review; schizophrenia

Abbreviation: IQ, intelligence quotient.

INTRODUCTION

Schizophrenia is a chronic psychiatric disorder of uncertain etiology, with peak incidence during the third decade of life. Hundreds of clinical studies have demonstrated impaired neuropsychological functioning in patients with schizophrenia (1). However, the vast majority of these have used case-control designs comparing clinical samples of schizophrenic patients with controls on measures of current cognitive functioning. The difficulty with interpreting these studies is that any deficits found could have arisen through any combination of at least seven possible mechanisms.

1. Cognitive deficits could be direct, causal risk factors for schizophrenia.
2. The deficits could be associated with factors that are involved in the etiology of schizophrenia but not causal themselves.
3. They could be early symptoms of the disorder itself, which predate the onset of psychotic symptoms.
4. They could be core symptoms of the disorder that arise concurrently with the onset of psychotic symptoms.
5. They could be a consequence of the symptoms of schizophrenia, such as auditory hallucinations, agitation, or apathy.
6. They could be the adverse effects of drug treatment for schizophrenia.
7. They could be secondary to the chronically impoverished social and occupational environment of many patients with schizophrenia.

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Retrospective case-control studies are generally unable to distinguish among these possibilities. First, they are susceptible to selection bias. Cases may be atypical, perhaps higher functioning or more likely to be in contact with services. Controls may also be atypical of the population from which the cases arose. Second, case-control studies are potentially subject to observer bias, since the experimenter is aware of the illness status at the time of testing. Third, and most important, case-control studies are unable to distinguish between premorbid and illness-related cognitive deficits. This distinction has profound implications for the etiology of schizophrenia. If cognitive deficits are present before the onset of illness, particularly if they antedate the illness by some time, this would suggest that they are either directly causal or are associated with causal factors that are involved in etiology (mechanisms 1 or 2), rather than being secondary to the illness or its treatment.

Some case-control studies have used estimates of premorbid function, such as reading tests. However, these tests rely on current performance, so they are not immune to contamination by illness-related effects, and the tests of premorbid function that are used often have poor or unproven validity in schizophrenia (2).

To be clear whether deficits exist premorbidly, it is therefore vital to use unbiased, population-based data that were collected prospectively, prior to illness onset, with subsequent population-based monitoring for later schizophrenia. Only a small minority of studies have used truly prospective, population-based data. The main disadvantage of these studies is that exposure and outcome were not usually collected for the purposes of the study, so they are often of lower validity than in case-control studies. However, these studies have generally been of very large size and epidemiologic rigor. The aim of this paper is to review these studies and to assess their findings.

Search strategy

This review will include only studies that have used population-based cohort designs, with general intellectual functioning measured prospectively, before the onset of schizophrenia, and subsequent population-based monitoring for onset of schizophrenia. For a study to be included, the comparison group must consist of the entire population from which the sample was drawn (a population-based cohort study) or be a representative sample drawn from such a cohort (a nested case-control design).

MEDLINE and PubMed were searched using the terms (schizophrenia OR psychosis) AND (IQ [intelligence quotient] OR intelligence OR intellectual OR cognitive OR neuropsychological OR school OR scholastic OR academic) AND (prospective OR population OR cohort OR premorbid) from 1990 to 2007. The bibliographies of these papers were then hand searched for other relevant studies. Cohort studies and case-control designs nested within cohorts, in which the exposure was a measure of general intellectual functioning, and the outcome was the incidence or period prevalence of schizophrenia or schizophreniform disorder, were included. In some instances, several papers reported on different aspects of data from identical or overlapping cohorts. In these cases, the primary studies that reported incidence or period prevalence were included. Secondary studies, for example, on subgroups or focusing on the course or outcome of schizophrenia, were not included.

The studies fell broadly into three categories: birth cohort studies, army conscript studies, and school performance studies. The methodological details of the studies are summarized in table 1.

BIRTH COHORT STUDIES

National Survey of Health and Development (1946 birth cohort)

In 1994, Jones et al. (3) published a study on a stratified sample from a birth cohort of people born in a single week in 1946 and alive in the United Kingdom at age 16 years (n = 4,746). The members of the cohort were given a broad range of cognitive tests at the ages of 8, 11, and 15 years. They were then followed up between age 16 and age 43 years by regular contacts with the research team. In addition, a national register of admissions to psychiatric hospitals in Britain from 1974 to 1986 (the Mental Health Enquiry) was used to identify additional cases. There were 30 cases of schizophrenia overall.

Children who were to subsequently develop schizophrenia scored consistently lower on all measures of cognitive function, particularly on nonverbal tests, and there appeared to be an approximately linear association between cognitive score and risk for schizophrenia. This association did not appear to be confounded by socioeconomic group or sex. There was a tendency for the disparity between preschizophrenic and healthy individuals to increase with age.

National Child Development Survey (1958 birth cohort)

This survey followed a very similar design to that of the 1946 birth cohort discussed above, although it relied exclusively on the Mental Health Enquiry for retrieval of cases (4). The subjects were only 28 years of age at the end of follow-up, so the study was biased in favor of early onset cases. The 40 children who would go on to develop schizophrenia in adulthood showed a stable pattern of deficits at 7 and 11 years of approximately 0.6–0.7 standard deviations across a wide range of neuropsychological assessments and subjective teachers' ratings of school work.

Dunedin Multidisciplinary Health and Development Study

In the Dunedin Multidisciplinary Health and Development Study, a 1-year birth cohort from 1972 to 1973 was assessed at biennial intervals between ages 3 and 11 years on a range of emotional, behavioral, and interpersonal problems, motor and language development, and intelligence (5, 6). Study participants were asked about psychotic symptoms at the age of 11 years and were interviewed at 26 years, by using a diagnostic interview schedule. Only a small proportion met the criteria for schizophrenia, partly because of the requirement, under the *Diagnostic and Statistical*

Manual of Mental Disorders, Fourth Edition (DSM-IV), for 6 months' chronicity. The broader category of schizophreniform disorder was therefore used instead, yielding 36 cases.

There was a marked and significant difference between schizophreniform disorder cases and the remainder of the cohort for both intelligence quotient (IQ) and receptive (but not expressive) language at the ages of 3, 5, 7, 9, and 11 years. Similar patterns were observed for noncognitive indicators of development, including motor skills and neurologic signs. These associations did not change after adjusting for obstetric complications. A further finding was that children who reported isolated psychotic symptoms at 11 years of age had a significantly lower IQ and receptive language development in the first decade of life than did unaffected individuals.

CONSCRIPT STUDIES

Swedish conscript studies

David et al., 1997. In 1997, David et al. (7) pubished data from 50,000 males conscripted into the Swedish Army from 1969 to 1970 at age 18 years, who underwent cognitive tests at conscription in four domains: mechanical and general knowledge and verbal and visuospatial ability. This was the first study of this type to make use of the Scandinavian registers of routinely collected data, which can be linked by means of the personal identification numbers carried by all citizens in most Scandinavian countries. The study linked data from the Swedish Army to the Swedish National Register of Psychiatric Care, which contained data on all admitted cases of schizophrenia in Sweden until 1984; 195 cases of schizophrenia were identified.

Overall IQ was highly predictive of schizophrenia, and this association persisted after controlling for socioeconomic status, behavioral adjustment in childhood, drug misuse, urban upbringing, family history of psychiatric disorder, and psychiatric disturbance at the time of testing. Mechanical knowledge showed the strongest association with schizophrenia and was the only one of four domains that remained significantly associated with schizophrenia after adjustment for the other three domains.

The authors also compared the distributions of scores in patients and the population. There was some evidence that the risk in the lowest category was greater than would have been expected in a linear association, although a likelihood ratio test for departure from linear trend was not significant.

Zammit et al., 2004. In 2004, the authors extended the original study in three ways (8). First, they used data from the Swedish National Hospital Discharge Register to 1996, which identified almost twice as many ($n = 362$) cases of hospitalized schizophrenia as their previous study did. Second, they expanded the outcomes to include bipolar affective disorder, severe depression, and other psychoses. Third, they used a survival analysis (Cox regression) that took account of censoring, although they found that this did not substantially alter the results, and reported odds ratios obtained using logistic regression.

The association between test scores and schizophrenia was very similar to that seen in the earlier study, and again, mechanical ability was the strongest predictor. ''Other psychoses'' followed a similar pattern.

Gunnell et al., 2002. Gunnell et al. (9) performed a similar study, using a larger data set but a shorter follow-up. The cohort comprised 109,643 males who were conscripted between 1990 and 1994, with follow-up using the National Hospital Discharge Register to the end of 1997 to identify 60 cases of schizophrenia and 92 cases of nonaffective, nonschizophrenic psychosis. Because subjects were followed for a mean of only 5 years from the age of 18 years, there was a strong bias toward early onset cases. By means of linkage to the Swedish Medial Birth Register, the authors were able to control for birth weight, birth length, gestational age, Apgar score, maternal age, and parity, as well as parental educational level. They used a survival analysis (Cox proportional hazards).

As in many previous studies, poor scores strongly predicted schizophrenia and, to a lesser extent, other nonaffective psychoses. There was no evidence of confounding by pregnancy or birth variables. Of the cognitive domains, the technical and logic scores were the strongest predictors of schizophrenia, but all domains were predictive.

Although strictly outside the scope of this review, a fascinating finding was that the strongest predictor of both schizophrenia and nonaffective psychosis, which also showed the greatest discrimination between schizophrenia and other nonaffective psychoses, was a subjective score indicating suitability for officer status, based on a structured interview by a psychologist. This suggests that the typical preschizophrenia deficit may be better captured by a subjective assessment incorporating a range of global cognitive and social competencies rather than by any specific cognitive test.

Israeli conscript studies

Davidson et al., 1999. Like the Scandinavian countries, Israel has a well-developed system of registers that can be linked by using national identification numbers. This was a nested case-control study, in which 509 patients with schizophrenia were matched on age, gender, and school to 9,215 controls; each case was matched to the mean score of the remainder of his class, and the analysis was a matched design using conditional logistic regression (10). As with the Swedish studies, only boys were included. Conscription occurred at the age of 16–17 years between 1985 and 1991, and follow-up continued until 1995, when the cohort members were aged approximately 20–28 years. Schizophrenic patients performed significantly worse than controls did. Although unremarked by the authors, there was an excess of schizophrenic patients in the highest two performance bands. There was no statistical test as to whether this excess was likely to be a chance finding, although a test for departure from linear trend was not significant.

As well as test scores, a variety of behavioral measures, such as social functioning, organizational ability, interest in physical activity, and individual autonomy, were also strongly associated with risk of schizophrenia.

Reichenberg et al., 2002. The authors then extended the findings from the previous study in several ways (11).

TABLE 1. Methodological details of the studies included

Author(s), year (reference)	Cohort	Cohort type	Study design	Country	No. in cohort	No. with schizophrenia	Age(s) at premorbid testing (years)	Follow-up to age (years)	Outcomes	Diagnostic definition
Jones et al., 1994 (3)	National Survey of Health and Development (British 1946 birth cohort)	National birth cohort	Cohort study	United Kingdom	4,746	30	8, 11, 15	43	National admissions register plus follow-up interviews	DSM-IIIR* schizophrenia or schizoaffective disorder
Done et al., 1994 (4)	National Child Development Survey (British 1958 birth cohort)	National birth cohort	Nested case-control study	United Kingdom	12,537 (1,914 controls)	40	7, 11	28	National admissions register plus examination of case records	PSE/CATEGO* schizophrenia
Cannon et al., 2002 (5) and 2006 (6)	Dunedin Multidisciplinary Health and Development Study	Regional birth cohort	Cohort study	New Zealand	1,036	36	3, 5, 7, 9, 11	26	Diagnostic Interview	DSM-IV* schizophreniform disorder
David et al., 1997 (7)	Army conscripts, 1969–1970	National cohort (healthy males)	Cohort study	Sweden	50,087	195	18	31	National Register of Psychiatric Care	ICD-8* schizophrenia
Zammit et al., 2004 (8)	Army conscripts, 1969–1970	National cohort (healthy males)	Cohort study	Sweden	50,087	362	18	44	National inpatient discharge register	ICD-8, ICD-9* schizophrenia or schizoaffective disorder
Gunnell et al., 2002 (9)	Army conscripts, 1990–1994	National cohort (healthy males)	Cohort study	Sweden	109,643	60	18	21–27	National inpatient discharge register	ICD-9-, ICD-10* schizophrenia
Davidson et al., 1999 (10)	Army conscripts	National cohort (healthy males)	Matched nested case-control study	Israel	9,215 controls (cohort size not specified)	509	16–17	20–28	National inpatient admission register	ICD-9 schizophrenia
Reichenberg et al., 2002 (11)	Army conscripts	National cohort (includes females)	Matched nested case-control study	Israel	536 controls (1:1 matching; cohort size not specified)	536	16–17	17–29	National inpatient admission register	ICD-9 schizophrenia
Tiihonen et al., 2005 (12)	Army conscripts	National cohort (healthy males)	Cohort study	Finland	195,019	621	19–20	25–30	National inpatient discharge register	ICD-8, ICD-9 schizophrenia
Isohanni et al., 1998 (13)	Northern Finland 1966 Birth Cohort	Regional birth cohort	Cohort study	Northern Finland	11,017	89	14, 16	28	National inpatient discharge register	DSM-IIIR schizophrenia
Cannon et al., 1999 (15)	Helsinki 1951–1960 birth cohort	Regional birth cohort	Nested case-control study	Helsinki, Finland	408 (controls)	400	7–11	30–40	National inpatient discharge register	DSM-IIIR schizophrenia
MacCabe et al., in press (16)	Swedish national schools register	National cohort	Cohort study	Sweden	715,401	493	15−16	17–41	National inpatient discharge register	ICD-9, ICD-10 schizophrenia

* DSM-IIIR, *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised; PSE/CATEGO, a computer algorithm for generating diagnostic categories based on the responses to the Present State Examination; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; ICD-8, *International Classification of Diseases*, Eighth Revision; ICD-9, *International Classification of Diseases. Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death,* Ninth Revision; ICD-10, *International Statistical Classification of Diseases and Related Health Problems,* Tenth Revision.

First, the size of the sample was increased, by adding another four annual cohorts (up to 1995) and extending follow-up by 1 year (to 1996). Second, by focusing only on cognitive tests, which were taken by both sexes, females could also be included. Third, the authors examined the subtests from the cognitive battery. Again, the design was a nested case-control study, this time with conventional one-to-one matching on age, sex, and school. Preschizophrenic patients showed significant deficits in all measures.

Finnish conscript study

This study used a design similar to those of the Swedish and Israeli conscript studies (12). Of all the males born from 1962 to 1967, the 195,000 who served in the Finnish Army between 1982 and 1987 (87 percent) were tested at a mean age of 20 years and followed with the Finnish Hospital Discharge Register until the end of 1991, when they were aged 24–29 years.

A poor performance on a test of visuospatial reasoning predicted higher risks of schizophrenia, but arithmetic reasoning and verbal reasoning do not appear to have predicted schizophrenia from the data presented; none of the performance categories differed significantly from the reference category, but the odds ratios for trend were not given.

SCHOOL PERFORMANCE STUDIES

Northern Finland 1966 birth cohort

This cohort of 11,000 individuals, with prospectively collected information on school performance, was followed by using the Finnish Hospital Discharge Register until 1994, when the cohort members were 28 years of age (13). The outcomes of interest were schizophrenia, other psychoses, and nonpsychotic psychiatric disorders.

The authors used two measures of poor school functioning: a categorical variable indicating that the student was not in his expected class at 14 years of age and the grade-point average achieved at age 16 years among those who were in their normal class. As expected, being in a lower class than expected was a significant risk factor for schizophrenia (odds ratio = 2.5, 95 percent confidence interval: 1.2, 5.1), but surprisingly, there was an even greater effect for other psychoses and for nonpsychotic mental disorders. Furthermore, among children who were in their normal class at age 16 years, children who would later develop schizophrenia did not differ in their grade-point average from those who would remain well. The same negative result applied to other psychoses, but children with future nonpsychotic disorders had significantly worse grades than did the population.

It is difficult to explain why the performance of nonpsychotic patients was actually worse than that of schizophrenic patients. However, it should be noted that these were admitted cases. Although almost all cases of schizophrenia are admitted at some point in the early course of the disorder, this may not be the case for nonpsychotic disorders, so one would expect that the few cases of nonpsychotic disorders in this study were particularly severe, whereas the schizophrenia cases were probably more representative. Nevertheless, this study suggests that poor school performance may not be specific to schizophrenia.

Another unexpected finding was that boys with excellent school performance at the age of 16 years had a fourfold increased risk of schizophrenia compared with controls. However, the numbers were small, and if two fewer cases of schizophrenia had occurred in the excellent performance group, the result would not have been statistically significant. Furthermore, the effect was completely absent in girls (14) and was significant only if girls were excluded.

Helsinki cohort

This was a nested case-control study within the cohort of all children born in Helsinki during a 10-year period, 1951–1960 (15). The authors used the Finnish Hospital Discharge Register, pensions register, and free medicines register to identify nonhospitalized, as well as hospitalized, cases of schizophrenia (broadly defined as code 295 in the *International Classification of Diseases,* Eighth Revision (ICD-8) and Ninth Revision (ICD-9)) who were born in Helsinki. School grades and teachers' ratings at the ages of 7–11 years were identified for just under half of these children and compared with those of Helsinki-born controls. Principal components analysis identified three factors from the scores: academic, nonacademic, and behavioral.

Again, there was an unexpectedly small difference between cases and controls. They differed only on the behavioral measure, which accounted for 11 percent of the total variance and loaded mainly sports and handicraft. There was no difference in class rank between cases and controls, although cases were less likely to proceed to high school at the age of 11 years.

Swedish schools register study

Using a national sample of 907,011 individuals born in Sweden between 1973 and 1983, this study (16) utilized Cox proportional hazards regression to assess whether scholastic achievement at the age of 15–16 years predicted hospital admission for schizophrenia (obtained from the Swedish Hospital Discharge Register) and nonaffective psychoses between 17 and 31 years of age.

A grade-point average of at least 2 standard deviations below the population mean was associated with an increased rate of schizophrenia (hazard ratio = 3.87, 95 percent confidence interval: 2.80, 5.34), compared with children within 1 standard deviation of the mean. Furthermore, the results were consistent across all school subjects, such that receiving the lowest grade of ''E'' was independently associated, at the $p < 0.001$ level, with risk for schizophrenia in every one of 16 compulsory school subjects. The association appeared linear, and a higher grade-point average had a protective effect. There was no evidence of confounding by migrant status, low birth weight, hypoxia, parental educational level, or socioeconomic group.

SUMMARY AND CONCLUSIONS

Almost all studies have found a generalized deficit affecting most or all domains, with no clear pattern of differential

deficits. The effect does not seem to be driven by subgroup of schizophrenic individuals with particularly low ability; rather, the decrement in cognitive ability is evenly distributed across the range of ability in the population.

The two Finnish studies on school performance are unique in failing to find large deficits in preschizophrenic children, although subtle differences did emerge. Clearly, school performance is a less direct measure of specific cognitive functions (such as verbal memory) than well-designed neurocognitive tests that are specifically designed to test these functions. Nevertheless, a recent longitudinal study of 70,000 individuals showed that 50–60 percent of the variance in examination results at age 16 years could be explained by intelligence at age 11, indicating that these domains overlap substantially (17).

The Swedish study by our own group found strong associations between premorbid scholastic achievement and schizophrenia in all 16 compulsory school subjects. It is difficult to explain the discrepancy between this study and the Finnish studies. One possibility, suggested by the authors of the Helsinki study (15), is that the Finnish educational system may be particularly structured and supportive of children who are having difficulties.

The role of confounding in these associations needs to be explored further. Many of the known risk factors for schizophrenia are also risk factors for poor cognitive function. These include socioeconomic group, parental educational level, pregnancy and birth complications or abnormalities (18–20), season of birth (21), parental (particularly paternal) age at birth (22), and migration or minority status (23, 24). A few studies have adjusted for some or all of these confounders, and most find little evidence of confounding (16). However, the possibility of unmeasured and residual confounding remains.

The strong associations between cognitive impairments in childhood and adolescence and risk of later schizophrenia suggest that cognitive dysfunction is related to the etiology of schizophrenia. It is possible that low intelligence could directly predispose to psychosis: For example, people with lower intellectual ability may be less easily able to reject delusional ideas than more intelligent individuals. The data are also consistent with the possibility that social or psychological risk factors, such as long-term psychological stress or even styles of family interaction, could account for the association. Arguably the explanation that fits best with the available evidence from other studies (25) is that schizophrenia is a disorder of abnormal neurodevelopment. This is consistent with epidemiologic evidence that schizophrenia is associated with early developmental insults, such as low birth weight, neonatal asphyxia (26), and prenatal viral infections (27), as well as a range of premorbid social and motor deficits (5).

It is now beyond reasonable doubt that schizophrenia is associated with premorbid cognitive deficits. Future research should not focus on replicating this finding but on exploring the nature and timing of premorbid deficits, the effect of confounding variables, the associations between cognitive deficits and known genetic or environmental risk factors, and the relation between premorbid cognitive function and the clinical course and outcome of schizophrenia.

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