ORIGINAL ARTICLE

A Longitudinal Study of Premorbid IQ Score and Risk of Developing Schizophrenia, Bipolar Disorder, Severe Depression, and Other Nonaffective Psychoses

Stanley Zammit, MRCPsych; Peter Allebeck, MD; Anthony S. David, PhD; Christina Dalman, MD; Tomas Hemmingsson, PhD; Ingvar Lundberg, MD; Glyn Lewis, PhD

Context: Longitudinal studies indicate that a lower IQ score increases risk of schizophrenia. Preliminary evidence suggests there is no such effect for nonpsychotic bipolar disorder. To our knowledge, there are no prior population-based, longitudinal studies of premorbid IQ score and risk of developing severe depression requiring hospital admission.

Objectives: To investigate the association between premorbid IQ score and risk of developing schizophrenia, other nonaffective psychoses, bipolar disorder, and severe depression and to investigate effects of confounding and examine possible causal pathways by which IQ may alter these risks.

Design: Historical cohort study, using record linkage for hospital admissions during a 27-year follow-up period.

Setting: Survey of Swedish conscripts (1969-1970).

Participants: Population-based sample of 50087 male subjects. Data were available on IQ score at conscription and on other social and psychological characteristics.

Main Outcome Measures: *International Classification of Diseases, Eighth Revision* or *Ninth Revision* diagnoses of schizophrenia, bipolar disorder, severe depression, and other nonaffective psychoses.

Results: There was no association between premorbid IQ score and risk of bipolar disorder. Lower IQ was associated with increased risk of schizophrenia, severe depression, and other nonaffective psychoses. Risk of schizophrenia was increased in subjects with average IQ compared with those with high scores, indicating that risk is spread across the whole IQ range.

Conclusions: Lower IQ score was associated with increased risk for schizophrenia, severe depression, and other nonaffective psychoses, but not bipolar disorder. This finding indicates that at least some aspects of the neurodevelopmental etiology of bipolar disorder may differ from these other disorders.

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From the Department of Psychological Medicine, University of Wales College of Medicine, Cardiff (Dr Zammit); Department of Social Medicine, Gothenburg University, Gothenburg, Sweden (Dr Allebeck); Institute of Psychiatry, King's College, London, England (Dr David); Department of Psychiatric Epidemiology, Stockholm Centre of Public Health, Stockholm, Sweden (Dr Dalman); Department of Public Health Sciences, Karolinska Institute, Stockholm (Drs Hemmingsson and Lundberg); and Division of Psychiatry, University of Bristol, Bristol, England (Dr Lewis).

THERE IS STRONG EVIDENCE that patients with schizophrenia show impairments in a wide variety of neuropsychological tasks, including attention, executive function, language, memory, and general intellectual ability.[1] Thus, when investigating risk factors for schizophrenia, case-control studies of premorbid cognitive ability may be particularly biased if this is assessed after onset of the disorder. Overall results from such studies for schizophrenia indicate that impairment in intellectual ability may exist from early in life and is not just a consequence of the pathological process of disease onset.[2]

Findings from population-based studies support this view. Jones et al,[3] using the 1946 birth cohort, found that subjects who developed schizophrenia were more likely to have had impairments in childhood educational scores that persisted after adjusting for sex and social class. David et al[4] found a strong association between IQ score at the age of 18 years and subsequent risk of developing schizophrenia in a cohort of male Swedish conscripts. In a separate Swedish conscript cohort, Gunnell et al[5] found that IQ was associated with risk of early-onset schizophrenia after adjusting for markers of prenatal adversity and obstetric complications. Lower verbal and nonverbal IQ scores at the age of 11 years were reported for subjects who developed schizophrenia in the National Child Development Study.[6] In the Dunedin birth cohort, children who developed a schizophreniform disorder in adulthood were also more likely to have worse childhood IQ scores and receptive language impairments.[7]

A recent nested case-control study of subjects drafted into the Israeli military ser-

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vice found that subjects who later developed schizophrenia showed highly significant impairments in premorbid adolescent intellectual function and reading tasks compared with controls.[8] Controls were matched for sex, high school attendance, and age at assessment. Subjects with schizoaffective disorder also showed significant impairments in 1 of the 4 subtests of intellectual performance, although the small numbers in this group may have limited statistical power to observe significant differences in the other subtests measured. Another population-based, nested case-control study,[9] however, found no association between school academic performance and risk of schizophrenia. Although this study was well powered, school education results may reflect intellectual ability less adequately than IQ score does.

Cognitive ability in bipolar disorder has been less well studied, but there are reasonably consistent findings that subjects with this disorder also show evidence of cognitive impairments after onset of the illness.[10,11] These deficits are observed even when subjects are euthymic, although impairments are more marked when affective symptoms are present. The few studies that adjust for residual affective symptoms show evidence for impairments, mainly in verbal learning and memory and sustained attention during remission.[10,11]

Studies of premorbid intellectual functioning in subjects who develop bipolar disorder show some variation in results. In the 1946 birth cohort, van Os et al[12] found an association between childhood cognitive ability and risk of both childhood and adult-onset affective disorders. In a case-control design, Gilvarry et al[13] found that affective psychosis subjects had significantly lower premorbid IQs, as estimated by the National Adult Reading Test (NART), than their first-degree relatives but premorbid IQs that were not different than those of controls. Selection of controls from job centers may have biased the comparison with the control group. Neither of these studies distinguished between unipolar and bipolar disorders, making the association between premorbid intellect and bipolar disorder difficult to interpret. A comparison of NART scores among subjects with bipolar disorder found that subjects were no different from controls but performed significantly better than subjects with schizophrenia.[14] In an early cohort study of US Army recruits, Mason[15] found that subjects who developed a manic-depressive disorder had a significantly raised IQ score at induction vs noncases. It is unclear what the criterion for diagnosis of manic depression was in this study, but it was probably a clinical diagnosis. No other study since has replicated this observation of a raised premorbid IQ in this patient group.

Two additional case-control studies[16,17] found no difference in NART scores between euthymic bipolar patients and controls. Goldberg et al[18] found no difference in premorbid IQ as measured by the Wide Range Achievement Test–Revised reading test between subjects with bipolar disorder and those with either unipolar depression or schizophrenia. Sample sizes were small for all these studies (approximately 20 subjects), and statistical power is likely to have been limited. Similarly, in the Dunedin birth cohort, there was no association observed between childhood IQ or language measures and risk of developing bipolar disorder (N = 20).[7] However, the confidence intervals (CIs) narrowly overlap with those for schizophrenia, suggesting that a difference between the 2 disorders may exist for measures of premorbid intellect. Furthermore, Reichenberg et al[8] found no association with premorbid intellectual or language measures for 68 subjects with nonpsychotic bipolar disorder.

Comparisons between subjects with schizophrenia and bipolar disorder on postmorbid tests of cognitive function show that those with schizophrenia perform consistently worse than those with bipolar disorder.[11,19] In both disorders, though there is a wide variation in study results, subjects seem to perform more poorly on performance-based rather than verbal-based neurocognitive tests.[1,11]

A limitation of many studies to date has been the difficulty of untangling effects of IQ score on risk of bipolar disorder as opposed to affective disorders in general. This is important given the theoretical implications of a separate pathogenesis for the 2 disorders. It is also unclear whether intellectual function is associated with risk of psychosis per se, regardless of the diagnosis. For example, Gunnell et al[5] found an association between IQ score and nonaffective psychoses, whereas David et al[4] found an association between IQ and nonschizophrenia psychotic disorders that included subjects with affective psychoses.

Furthermore, few studies have examined the possible role of confounding as a possible explanation for associations between IQ and psychiatric diagnoses. The aim of this study was to further examine the association between premorbid IQ score and risk of developing bipolar disorder, severe depression, schizophrenia, and other psychotic disorders in men. Specifically, we wanted to (1) examine the relationship between premorbid IQ score and risk of developing bipolar disorder by studying a larger sample of cases than previous studies and by including subjects both with and without psychotic symptoms; (2) examine whether it is specifically low IQ score that increases risk of schizophrenia or whether even average IQ is associated with increased risk compared with high-scoring subjects; (3) investigate the effect of premorbid IQ score on risk of developing other nonaffective psychoses and depression severe enough to warrant hospital admission; (4) investigate the effect of potential confounders on the relationship of these disorders with IQ score, including drug use, paternal age, family history, social class, and nonpsychotic psychiatric disorders at the age of 18 years; (5) investigate possible causal pathways by which IQ score may operate to alter risk of developing these disorders; and (6) investigate the relationship between premorbid IQ score and age at onset, number of admissions, and total days of admission as markers of illness severity.

METHODS

SUBJECTS

The cohort consisted of 50 087 Swedish men conscripted for compulsory military training during 1969-1970. More than 98% were 18 to 20 years of age. Only 2% to 3% of the male popu-

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Table 1. Summary of Confounders According to IQ Score at Conscription

	Cohort Sample, *No. (%)			
IQ	Diagnosis on Conscription†	Disturbed Behavior‡	Drug Use	Raised in City
Low IQ (n = 9540)	1481 (16)	646 (7)	769 (8)	1430 (15)
Medium IQ (n = 24 668)	2573 (10)	1181 (5)	2978 (12)	5003 (20)
High IQ (n = 15 793)	1100 (7)	408 (3)	2055 (13)	3912 (25)

*IQ score data were missing for 86 subjects.
†Any psychiatric disorder except psychosis or learning disability.
‡Disturbed behavior is defined as a score greater than 95th percentile.

lation were excused conscription on account of severe mental or physical disability. This is the same cohort used by David et al,[4] who examined the relationship between IQ score and risk of both schizophrenia and other psychoses. However, we now have additional cases identified due to a longer follow-up period, and we also investigate other psychotic diagnoses separately.

The conscription procedure included tests of intelligence and nonanonymous, self-reported questionnaires on family, social background, behavior during adolescence, and substance use. All subjects underwent a structured interview conducted by a psychologist, and those reporting any psychiatric symptoms were interviewed by a psychiatrist and given a diagnosis according to the *International Classification of Diseases, Eighth Revision* (*ICD-8*)[20] when applicable. Thirty-four cases of psychosis diagnosed at conscription were excluded from the study, resulting in a sample size of 50 053. Permission to use the anonymized database was granted by the Karolinska Institute Research Ethics Committee and the Swedish Data Inspection Board.

INTELLECTUAL TESTS

There were 4 main subtests to the assessment of intelligence, each yielding a 9-point summary score. These subtests assessed verbal IQ, visuospatial ability, general knowledge and intelligence, and mechanical knowledge. Further details of these subtests are given in a previous study using this cohort.[4] These 4 subtests were aggregated to give an overall standardized intelligence score, ranging from 1 to 9 and corresponding to approximate IQ bands of less than 74, 74 through 81, 82 through 89, 90 through 95, 96 through 104, 105 through 110, 111 through 118, 119 through 126, and more than 126.

FOLLOW-UP

The Swedish National Hospital Discharge Register recorded approximately 70% of all psychiatric admissions in 1970, increasing to 83% in 1973. Coverage was 97% in 1974-1983 and 80% to 95% in 1984-1986 and has been virtually complete since 1987. The linkage reported herein was from 1970-1996. The incomplete registration during some periods is unlikely to have affected the results.

Patients were given clinical diagnoses according to the Nordic version of *ICD-8* (*ICD-9* from 1987). Satisfactory validity of schizophrenia diagnoses in Sweden have been previously reported.[21,22] Outcomes investigated were (1) schizophrenia (schizophrenia/schizoaffective disorder, *ICD-8* and *ICD-9:* 295.00-99), (2) bipolar disorder (manic-depressive psychosis, manic/circular type, *ICD-8:* 296.1, 296.3, 298.1; *ICD-9:* 296.0, 296.2-5, 298.1), (3) severe depression (manic-depressive psychosis, depressed type, *ICD-8:* 296.0, 296.2, 298.0; *ICD-9:* 296.1, 298.0), and (4) other nonaffective psychoses (paranoid states, other psychoses, substance-induced psychoses, *ICD-8:* 297.0-9, 298.2-3, 298.9, 291.2-3; *ICD-9:* 297.0-9, 298.2-4, 298.8-9, 291.3, 291.5, 292.1). Where subjects had 2 or more different psychotic diagnoses during the follow-up period, the following approach was used: if 1 diagnosis clearly dominated the admission diagnoses, this was the one used. However, if there was a roughly equal distribution of 2 or more diagnoses, a hierarchical approach was used. The diagnostic hierarchy was as follows: schizophrenia, schizoaffective disorder, bipolar disorder, other psychoses, and severe depression. Age at first admission was investigated as a proxy measure of age at illness onset. The number of psychiatric admissions and total duration of admissions in days for each individual were recorded as crude measures of illness severity to allow investigation of this phenotype with IQ score.

STATISTICAL ANALYSIS

Logistic regression was used to calculate odds ratios (ORs) and 95% CIs for the different diagnoses given IQ score both before and after adjustment for potential confounders. Although a small number of subjects died during follow-up, analysis using Cox regression, which takes into account such losses, made no differences in the results. Logistic regression was therefore retained as the method of choice. The relationship between IQ score and age at onset was examined using a linear regression model. The relationship between IQ score and number and severity of admissions was examined using Spearman rank correlation coefficients.

Variables previously shown to be associated with risk of schizophrenia and examined as potential confounders in the relationship between IQ and risk of disease were psychiatric diagnosis at conscription,[23] drug use,[24] place of upbringing,[25] and paternal age.[26] Disturbed behavior in childhood, family history of psychiatric illness, and father's occupation were also examined. Variables that were considered potential mediators of the relationship between IQ and risk of disease (ie, lying on the causal pathway) included drug use[24] and personality variables concerned with interpersonal relationships.[27] Only 3% of the sample had missing data for any of the questions.

RESULTS

Of the 50 053 male subjects, 362 (0.72%; 95% CI, 0.65%-0.80%) had developed schizophrenia by 1996, 108 (0.22%; 95% CI, 0.15%-0.25%) had developed bipolar disorder, 113 (0.23%; 95% CI, 0.19%-0.28%) had developed severe depression, and 223 (0.45%; 95% CI, 0.39%-0.51%) had developed nonaffective psychoses. IQ test results were available for all cases and were missing for 86 (0.2%) of noncases ($P = .43$). Of the 7 variables initially investigated as potential confounders or mediating variables, only 4 had any effect on the adjusted results and were used in the final analyses. A summary of these in relation to IQ is presented in **Table 1**. For the purposes of Table 1 *only*, IQ was split into 3 categories, and disturbed behavior was treated as a dichotomous variable, using the 95th percentile as a cutoff point for coding. The 4 intelligence subtests were all correlated with each other. The strongest correlation was between verbal IQ and gen-

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eral knowledge (r=0.75), and the weakest was between visuospatial ability and mechanical knowledge (r=0.50).

The 9-point aggregate IQ test score (**Table 2**) was associated with risk of developing schizophrenia (adjusted OR, 1.26; 95% CI, 1.19-1.33; P<.001). Of the 4 intelligence subtests, reduced performance for verbal IQ, visuospatial ability, and mechanical ability were associated with increased risk of schizophrenia that persisted after adjusting for the other subtest measures (**Table 3**). The largest increase in risk of developing schizophrenia was for subjects with the lowest IQ scores (**Figure**).

Omitting subjects with an IQ score below the mean, subjects with an average IQ had a significantly greater risk of developing schizophrenia than those with the highest IQ (OR, 1.3; 95% CI, 1.04-1.54; P=.02). Examination of whether a nonlinear relationship (within the logistic regression model) between IQ score and schizophrenia provided a better fit for the data was made by inclusion of a quadratic term (likelihood ratio test [LRT], χ^2_1=2.88, P=.09).

Although schizoaffective disorders are included in the schizophrenia group, we also looked at the specific relationship between IQ and this disorder. There were 35 subjects who developed schizoaffective disorder (0.07%; 95% CI, 0.05%-0.07%). Lower IQ scores were associated with an increased risk of developing schizoaffective disorder (adjusted OR, 1.40; 95% CI, 1.16-1.67; P<.001). In the subtest analyses, reduced performance for verbal IQ, visuospatial ability, and mechanical ability were associated with increased risk of schizoaffective disorder, similar to schizophrenia. These became nonsignificant after adjusting for the other subtest measures.

There was no evidence that aggregate IQ score during adolescence was associated with subsequent risk of developing bipolar disorder (adjusted OR, 0.99; 95% CI, 0.89-1.09; P=.78). However, lower IQ score was associated with risk of developing severe depression (adjusted OR, 1.19; 95% CI, 1.09-1.31; P<.001) and risk of other nonaffective psychoses (adjusted OR, 1.24; 95% CI, 1.15-1.33; P<.001).

Examination of the 4 intelligence subtests showed that there were no significant associations for any of the subtests and risk of developing bipolar disorder in either the crude or adjusted analyses. Performances for all 4 tests, however, were associated with risk of developing severe depression or other nonaffective psychoses. After adjusting for the other subtest scores, the associations between severe depression and mechanical ability and between other nonaffective psychoses and both mechanical ability and verbal IQ persisted.

Of subjects with bipolar disorder, 25 had an additional diagnosis of a psychotic illness (schizophrenia or other nonaffective psychoses) at some point during the follow-up period. The relationship with aggregate IQ score for these individuals was also investigated (OR, 0.97; 95% CI, 0.80-1.18; P=.76).

Comparison of mean±SD aggregate IQ score for subjects developing bipolar disorder (5.1±2.1) compared with the 3 other diagnostic categories grouped together (4.3±2.1) was performed using analysis of variance ($F_{1,791}$=12.1, P<.001). There were no significant differences in IQ score among any of the 3 other diagnostic categories (schizophrenia, 4.3±2.1; nonaffective psychoses, 4.3±2.1; severe depression, 4.5±2.1).

Table 2. Crude and Adjusted ORs (95% CIs) for Developing Psychiatric Disorders in 50 053 Subjects According to Premorbid IQ Score

Disorder	Subjects, No. (%)	OR (95% CI)	
		Crude	Adjusted*
Schizophrenia	362 (0.72)	1.29 (1.23-1.36)	1.26 (1.19-1.33)
Bipolar	108 (0.22)	1.07 (0.98-1.17)	0.99 (0.89-1.09)
Severe depression	113 (0.23)	1.22 (1.12-1.33)	1.19 (1.09-1.31)
Other psychoses	223 (0.45)	1.28 (1.20-1.37)	1.24 (1.15-1.33)

Abbreviations: CI, confidence interval; OR, odds ratio.
*The OR of 1.26 is interpreted as the increase in risk for each successive IQ category. Because IQ score is coded on a 9-point scale, the OR for schizophrenia comparing the lowest IQ with highest IQ (baseline) subjects is 1.26^8 = 6.35.

Results for the relationship between IQ score and age at onset, number of admissions, and duration of hospitalization for each of the diagnostic categories are presented in **Table 4**. There were no significant associations between these clinical markers and the disorders investigated. A nonlinear relationship between IQ score and age at onset was also investigated to try to further distinguish between premorbid effects of IQ and possible prodromal effects on score results by inclusion of a quadratic term into the model (schizophrenia LRT, χ^2=0.15, P=.70; bipolar disorder LRT, χ^2=2.8, P=.10; severe depression LRT, χ^2=1.5, P=.22; nonaffective psychoses LRT, χ^2=0.80, P=.37).

COMMENT

Premorbid IQ score was associated with risk of developing schizophrenia, schizoaffective disorder, other nonaffective psychoses, and severe depression in men. However, risk of developing bipolar disorder was not associated with premorbid IQ levels. The effect of IQ score on risk of these disorders was not mediated through or confounded by any of the other variables investigated in this study.

DIAGNOSTIC OUTCOMES

These findings add to the results of Reichenberg et al,[8] who found no association between adolescent IQ score and subsequent development of nonpsychotic bipolar disorder. In our study, the bipolar group is likely to have included subjects both with and without psychosis, because formal separation of these was not possible due to the classification system used during the study period. However, in the subset of bipolar subjects who had also been given a psychotic diagnosis at some point, there was no evidence for an association with premorbid IQ score, although the number of subjects in this group meant that statistical power was rather limited.

The evidence that reduced intellectual performance is associated with bipolar disorder *after* onset of the illness suggests that this may be due to either damage caused by disease onset or the effects of psycho-

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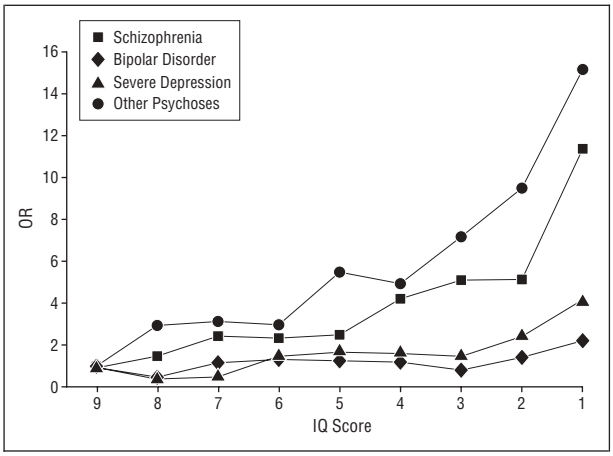
Table 3. Crude and Adjusted ORs (95% CIs) for Risk of Developing Psychiatric Disorders for the 4 Intelligence Subtests

	OR (95% CI)							
	General Knowledge		Verbal IQ		Visuospatial Ability		Mechanical Ability	
Disorder	Crude	Adjusted*	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted
Schizophrenia	1.22 (1.16-1.29)	0.94 (0.86-1.03)	1.25 (1.19-1.33)	1.10 (1.01-1.20)	1.25 (1.18-1.33)	1.07 (1.01-1.15)	1.37 (1.29-1.45)	1.25 (1.16-1.35)
Bipolar	1.09 (0.99-1.20)	1.02 (0.87-1.20)	1.07 (0.97-1.18)	0.98 (0.84-1.14)	1.05 (0.95-1.16)	0.97 (0.85-1.10)	1.08 (0.98-1.20)	1.03 (0.90-1.17)
Severe depression	1.18 (1.07-1.29)	1.02 (0.87-1.19)	1.16 (1.05-1.28)	1.00 (0.86-1.16)	1.20 (1.09-1.33)	1.08 (0.96-1.23)	1.24 (1.12-1.37)	1.15 (1.01-1.31)
Other psychoses	1.30 (1.21-1.39)	1.15 (1.03-1.29)	1.25 (1.17-1.34)	1.03 (0.92-1.15)	1.19 (1.11-1.28)	0.99 (0.91-1.08)	1.28 (1.20-1.37)	1.10 (1.00-1.21)

Abbreviations: CI, confidence interval; OR, odds ratio.
*Adjusted for the 3 other subtests. An OR of *x* is interpreted as the increase in risk for each successive IQ category. Because IQ score is coded on a 9-point scale for each subtest, the OR comparing the lowest IQ with highest IQ subjects is x^8.



Adjusted odds ratios (ORs) plotted against IQ scores for schizophrenia, bipolar disorder, severe depression, and other nonaffective psychoses. Highest IQ score (coded as 9) is the baseline category (OR=1.0).

tropic medication on test performance. It is also possible that the presence of affective or psychotic symptoms may affect cognitive performance, although impaired performance has been observed even after adjustment for residual symptoms.[10,11]

The relationship between premorbid intellectual function and risk of schizophrenia is already well established. The lack of evidence in our study for nonlinearity within the logistic regression model (which models the logarithm of odds) indicates that risk of schizophrenia increases exponentially with change in IQ score. However, our results also indicate that risk of schizophrenia was significantly increased in subjects with average IQ compared with those with high IQ scores. Risk is spread over the whole of the IQ spectrum, and it is not just low IQ score that is a marker of increased risk of developing schizophrenia. Put another way, higher IQ score could be said to protect against psychotic illness.

This study also confirms an association between low IQ score and increased risk of schizoaffective disorder. The effect size seems comparable to that of schizophrenia, suggesting that etiologically, schizoaffective disorder may be more akin to schizophrenia than bipolar disorder. A similar association was observed in one recent study[8] but not in another less well-controlled one that used the NART to estimate premorbid IQ.[13] Although all the subtest estimates in our study were nonsignificant, the trends were similar to those seen for schizophrenia, with the greatest effect being for the test of mechanical ability. The small number of subjects with schizoaffective disorder means that statistical power was limited for these analyses.

A strong association between IQ score and other nonaffective psychoses was also present. Although a similar finding was reported previously for this cohort,[4] in this secondary analysis subjects with affective psychoses were analyzed separately under bipolar disorder or severe depression, and new cases were also identified for analysis as a result of the longer follow-up period. Our results support the view that study of psychoses in general rather than schizophrenia in particular may be one way of increasing power to identify such shared risk factors among psychotic disorders.

This is the first population-based, longitudinal study to our knowledge that examines the relationship between premorbid IQ score and risk of developing depression severe enough to warrant hospital admission. Our results indicate that premorbid IQ score has a similar effect on risk for severe depression as for schizophrenia, schizoaffective disorder, and other nonaffective psychoses. Also, as for these other disorders, the strongest impairments seem to be in performance-based rather than verbal-based tests. Depression is a markedly heterogeneous disorder, and depression severe enough to warrant hospital admission is likely to represent an extreme of the disorder in which neurodevelopmental abnormalities, including intellectual development, may be more prone to occur.

One of the strengths of this study is the ability it affords us to assess confounding in the relationship between IQ and any of the outcomes investigated. There was no evidence of any strong confounding in this relationship. Furthermore, individual adjustments for drug use, disturbed childhood behavior, and social personality traits had no effect on the associations observed, indicating that they do not lie on the causal pathway between IQ score and risk of psychotic disorders. It is possible that IQ may either have a more direct effect on development of psychosis, perhaps by influencing cognitive interpretation of stimuli and events, or that IQ score may be a measurable marker of subtle cerebral disease

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Table 4. Comparison of Age at Onset, Number of Admissions, and Total Duration of Admissions According to IQ Score for Each Disorder

	Age at Onset*			No. of Admissions†			Total Duration of Admissions†		
Disorder	Median (Range), y	β (SE)	*P* Value	Median (Range)	Spearman ρ	*P* Value	Median (Range), d	Spearman ρ	*P* Value
Schizophrenia	27 (19-46)	0.02 (–0.28, 0.31)	.91	7 (1-80)	0.06	.23	359.5 (1-8581)	0.05	.33
Bipolar	32 (21-46)	0.08 (–0.05, 0.73)	.80	4 (1-71)	0.05	.62	79.5 (2-1600)	0.04	.68
Severe depression	39 (21-45)	–0.30 (–0.91, 0.32)	.34	1 (1-34)	0.03	.78	29 (1-348)	0.16	.10
Other psychoses	37 (21-46)	–0.14 (–0.55, 0.26)	.49	2 (1-37)	0.07	.27	16 (0-1670)	0.11	.11

*Linear regression model: the β coefficient is interpreted as the change in age at onset (in years) for each successive IQ category compared with highest (baseline) IQ score. For example, in subjects with schizophrenia, the change in age at onset between lowest IQ compare with highest IQ subjects is $0.02 \times 8 = 0.16$ years.

†Spearman rank correlation: ρ values greater than 0 indicate a relationship between decrease in IQ score and increase in number of admissions or total duration of admissions.

that itself influences development of psychotic symptoms. There is substantial evidence that neuroanatomical abnormalities occur in schizophrenia, depression, and bipolar disorder.[10,28-30] The results from the numerous neuroimaging studies are somewhat difficult to interpret given the often small sample sizes and marked heterogeneity in sample selection and methods, as well as the difficulties in separating premorbid and postmorbid effects. Nevertheless, there seems to be a substantial overlap in the pattern of abnormalities observed in the different disorders. However, there is also evidence to suggest important differences between bipolar disorder and both schizophrenia and depression, for example, in the hippocampus and amygdala, that might partly explain the differences in premorbid IQ scores observed in this study.[10,28,29]

The possibility of bias as an explanation for these results needs to be considered. Outcome misclassification is likely to be low for schizophrenia given that more than 90% of people with schizophrenia are admitted to a hospital at some point during their illness.[31] Subjects in the cohort with severe depression or bipolar disorder, however, are likely to be somewhat less representative of all such cases in the population, because admission to a hospital is less invariable. The results of such misclassification, if nondifferential with regard to IQ score, would be to underestimate any true associations between IQ and risk of developing these disorders. However, if subjects with low IQ are more likely than subjects with high IQ to be admitted to a psychiatric hospital, an overestimation of association between low IQ score and disease could occur. If this were the case, then we might expect a similar effect for subjects with bipolar disorder as for those with severe depression (ie, that an association with low IQ score would be present for both disorders). Although it is possible that subjects with depression are more likely to be admitted if they have low rather than high IQ, with an opposite relationship for bipolar subjects whereby admission is more likely for high rather than low IQ cases, this seems an unlikely scenario. The marked difference in the association with IQ score suggests that selection bias is not likely to be the main explanation for the disparity in results between these 2 disorders.

The use of clinical rather than operationally defined diagnoses would also tend to reduce differences between bipolar disorder and other psychotic disorders if such misclassification were random with respect to IQ score. However, information bias cannot be ruled out as a potential explanation if differential misclassification is present, for example, if subjects with bipolar disorder and low IQ scores were more likely than those with higher IQ scores to mistakenly receive a diagnosis of schizophrenia.

AGE AT ONSET AND ILLNESS SEVERITY

Structural abnormalities, such as ventricular enlargement and reduced brain volume, detected by neuroimaging techniques are more marked in subjects in whom schizophrenia commences in early childhood than in adolescence or adult life.[32] If such structural abnormalities are a marker of a more global cerebral insult that occurs from early life, it is reasonable to expect that IQ score may be more likely to be reduced in early onset or more severe cases. However, no association was observed between IQ score and age at onset or severity of illness as measured by number or duration of admissions. No adjustment for measures of social disadvantage at admission were made, although one would expect this confounder to result in, if anything, an increased association. Similarly, no association was observed between NART scores and age at onset of schizophrenia in 2 case-control studies,[13,33] although the latter reported an association between academic record and duration of hospitalization. It is possible that IQ score does not correlate strongly enough with anatomical abnormalities to make such an association detectable. Furthermore, other factors likely to contribute to IQ score may act independently of gross cerebral disease and reduce the power to observe these associations.

Examining markers of clinical severity also allows us to investigate the possible presence of selection bias. If low IQ were actually a risk factor for severity of illness rather than presence of illness per se, an apparent association between IQ and risk of psychotic disorders would arise if severe cases are more likely to result in hospital admission. The lack of association with illness severity suggests that such a bias is not an adequate explanation for these results.

We could not exclude the distinct possibility that IQ score is a risk factor for very early onset, that is, those

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with onset before conscription. The 34 cases with a psychotic disorder at conscription were, of course, excluded given the study design. Whereas for schizophrenia there seems to be no relationship between IQ score and age at onset, for severe depression, there is a suggestion that subjects with a low IQ may have a younger age of disease onset. One explanation may be prodromal effects of depression that result in reduced IQ scores at conscription.

Finally, one limitation to this study is the use of a nonpublished battery of tests, that used by the Swedish Army. Our descriptive labeling of the tests is to some extent arbitrary, and caution should be observed equating these with performance and verbal subtests of, for example, the Wechsler batteries. This limits comparability of these results with other studies. However, the fact that the entire population of men was administered the same battery allowed us to standardize the scores, which should compensate for this and aids interpretation.

In conclusion, this study indicates that premorbid IQ is likely to be a risk factor for psychotic illnesses in general rather than schizophrenia in particular. However, premorbid IQ score does not seem to have an effect on risk of developing bipolar disorder. Although extrapolating observational findings to underlying molecular mechanisms can only be theoretical in nature, these results nevertheless suggest that some aspects of the neurodevelopmental etiology of bipolar disorder are different from those for schizophrenia, nonaffective psychoses, and severe depression.

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Corresponding author: Stanley Zammit, MRCPsych, Department of Psychological Medicine, University Hospital of Wales, Cardiff CF14 4XN, Wales (e-mail: zammits@cardiff.ac.uk).

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