

# Elaboration on Premorbid Intellectual Performance in Schizophrenia

## *Premorbid Intellectual Decline and Risk for Schizophrenia*

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**Context:** Consistent evidence indicates that some, but not most, patients with schizophrenia have below-average intelligence years before they manifest psychosis. However, it is not clear whether this below-average premorbid intelligence is stable or progressive.

**Objective:** To examine whether increased risk for schizophrenia is associated with declining intellectual performance from childhood through adolescence.

**Design:** Historical cohort study of an entire population using record linkage for psychiatric hospitalization during an 8- to 17-year follow-up period.

**Setting:** Mandatory assessment by the draft board of Israeli conscripts.

**Participants:** Population-based cohort of 555 326 adolescents born in Israel. Data were available on 4 intelligence subtests as well as on reading and spelling abilities and on behavioral and psychosocial variables. A regression-based approach was used to assess the discrepancy between actual IQ at age 17 years and estimated IQ during childhood based on reading and spelling abilities.

**Main Outcome Measures:** Hospitalization for schizophrenia (as per the *International Statistical Classification of Diseases, 10th Revision* criteria).

**Results:** Lower-than-expected IQ at age 17 years was associated with increased risk for later hospitalization for schizophrenia. Results were held after controlling for potential confounders. For 75% of patients with schizophrenia with low actual IQ (<85) at age 17 years and for 23% of patients with actual IQ within the normal range ( $\geq 85$ ), actual IQ was 10 or more points lower than expected. Lower-than-expected IQ was not associated with bipolar disorder or with depression or anxiety disorder.

**Conclusions:** Indirect evidence suggests that intellectual deterioration from childhood through adolescence is associated with increased risk for schizophrenia. Despite within-normal-range premorbid IQ scores, apparently healthy adolescents who will later manifest schizophrenia nevertheless have intellectual decline.

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EVIDENCE EXISTS TO INDICATE that, as a group, individuals who later will be hospitalized for schizophrenia have intellectual deficits that predate the manifestation of psychotic symptoms.<sup>1-4</sup> However, there are inconsistent findings and divergent hypotheses as to the onset and course of the premorbid intellectual impairment. A majority of studies<sup>5-7</sup> indicate that intellectual deviations from norms are already present during childhood, and that the gap between individuals with future diagnoses of schizophrenia and normal individuals does not widen during this period (for a different view, see Kremen et al<sup>8</sup>). However, several lines of evidence from large retrospective

studies,<sup>9</sup> studies of clinical samples,<sup>10</sup> studies of high-risk individuals,<sup>11,12</sup> and family and twin studies<sup>13,14</sup> suggest that the deviations from intellectual norms might increase as the future patient moves from childhood into adolescence and approaches the onset of active psychotic illness. Only 2 population-based studies addressed this question. In a longitudinal study of the 1946 British birth cohort, Jones et al<sup>2</sup> found that the difference in intellectual performance between future patients and controls widens between ages 8 to 15 years. In contrast, no increase in the magnitude of impairment in future patients was found in the 1958 British birth cohort.<sup>15</sup>

Furthermore, despite group mean differences between future patients and con-

trols, in the majority of future patients with schizophrenia, mean test scores reflective of general intelligence (IQ) are within the normal range.<sup>3,16</sup> If cognitive abnormalities are, indeed, a core feature of the illness,<sup>17,18</sup> this would suggest that aspects of intellectual performance other than mean IQ scores might be relevant to the pathophysiological abnormalities of the schizophrenic illness. Studies<sup>19,20</sup> of clinical samples suggest that some patients with IQs within the normal range experience decline from the previous levels of intellectual functioning. Thus, increasingly larger deviations from intellectual norms may be a characteristic of future patients whose IQs fall within the normal range. To our knowledge, this has not yet been tested in an epidemiological cohort.

To examine change in premorbid IQ in future patients with schizophrenia, we used data collected during the mandatory assessments performed at age 17 years by the Israeli draft board. The data include assessments of language and IQ on almost all of the live births of Israeli-born Jewish persons during 10 consecutive years. The data were linked with psychiatric follow-up data provided by the Israeli National Psychiatric Hospitalization Case Registry (NPHCR). Language functions (reading and spelling), which are acquired early in life (at ages 6-8 years), were used to estimate intellectual potential in childhood, and change was estimated from the discrepancy between estimated intellectual potential during childhood and measured IQ scores at age 17 years.

## METHODS

### SUBJECTS

The study builds on the Israeli military draft board assessment of intellectual, medical, and psychiatric eligibility for service of the unselected population of Israeli-born Jewish adolescents aged 17 years as well as on the availability of the Israeli NPHCR. Some of the individuals included in this analysis were also used in case-control studies.<sup>4,21</sup> However, in addition to addressing different questions, the cohort in the present study is twice as large, had a longer follow-up period, and the present investigation uses a cohort design. The study was approved by the relevant local institutional review board committees.

### DRAFT BOARD ASSESSMENT

The population assessed by the draft board includes individuals who would be eligible for military service. It also includes those who will be exempted owing to medical, psychiatric, or social reasons.

### STANDARDIZED TEST MEASUREMENTS

The cognitive assessment conducted by the draft board consists of the assessment of language ability and intellectual functioning. These assessments are conducted by college-aged individuals who are trained in a 4-month course on the administration of draft board tests. The assessment and its validation are described in detail elsewhere.<sup>22</sup>

The assessment of language skills includes 4 subtests: (1) reading comprehension test, which measures the ability to understand ideas presented in unfamiliar passages of increasing length; (2) reading and vocabulary test, which measures the ability to correctly read and verify the meaning of single words; (3) spell-

ing ability test, in which the ability to spell increasingly difficult words is assessed (which is similar to the spelling subtests of the Wide Range Achievement Test); and (4) the examiner's overall impression of the fluency and quality of speech (ie, speaking ability). The vocabulary and spelling tests are individually administered. The reading comprehension test is group administered. Each of the 4 language tests is scored on a 5-point scale, and the sum of the scores provides a measure of language mastery.

The intellectual assessment includes 4 tests: (1) the instructions test, a modified, Otis-type verbal intelligence test adapted from the US Army Alpha Instructions Test, which measures the ability to understand and carry out verbal instructions (score range, 0-21); (2) verbal analogies, which is a modified version of the "similarities" subtest of the Wechsler Intelligence Scales that assesses verbal abstraction and categorization (score range, 0-30); (3) mathematical knowledge, which measures mathematical reasoning, concentration, and concept manipulation (score range, 0-25); and (4) nonverbal analogies, which is a modified version of Raven's Progressive Matrices that measures nonverbal abstract reasoning and visual-spatial problem-solving abilities (score range, 0-30). The tests are progressive, beginning with relatively simple questions and becoming more difficult. The tests are group administered and time limited. All of the scores are based on the number of correct answers. The sum of the scores for the 4 tests forms a validated measure of general intelligence (IQ),<sup>4,21,22</sup> scored on a 9-point scale. The correlation between the draft board scale and the Wechsler IQ scale was 0.79.<sup>23</sup>

## NATIONAL PSYCHIATRIC HOSPITALIZATION CASE REGISTRY

The Israeli NPHCR contains a complete listing of all of the psychiatric hospitalizations in Israel, and it includes the *International Statistical Classification of Diseases (ICD), 10th Revision* diagnoses assigned at admission and discharge by a board-certified psychiatrist. Diagnoses recorded in earlier ICD codes are routinely upgraded by the registry. All of the inpatient mental health facilities in the country, including day hospitals, are required by law to report admissions and discharges to the registry. Reporting is monitored by a special department at the Ministry of Health that verifies compliance with reporting and consistency of the information, ensuring the completeness and correctness of the data in the registry. Therefore, through the NPHCR, we were able to identify *all* of the currently and previously hospitalized cases of schizophrenia in the cohort. Registry diagnoses have shown good sensitivity and specificity when measured against research diagnosis.<sup>24</sup>

### DATA LINKAGE

The NPHCR was linked with the draft board registry by the managers of the NPHCR. The registry files were linked by using a method approved by local institutional review board committees to preserve medical record confidentiality. The linking variable was the unique individual Israeli identification number assigned to all of the citizens at birth or on award of citizenship. The merged file included data for all of the adolescents consecutively assessed by the draft board who were linked with the NPHCR. This allowed for a follow-up period of 8 to 17 years since the draft board assessment.

To limit this analysis to individuals with no obvious signs of psychotic illness during the draft board assessment, all of the adolescents who were assigned a psychotic psychiatric diagnosis by the draft board (as described below) or who had a psychiatric hospitalization at any time before the draft board assessment or within 1 year from the date of the draft board assessment were excluded. Also, individuals with mental re-

tardation were excluded. To test for specificity of the putative indices of intellectual decline to development of schizophrenia, similar methods were applied to identify adolescents assessed by the draft board during the same period who were later hospitalized with nonpsychotic bipolar disorder or with depression or anxiety disorder.

## ANALYTIC COHORT

Subjects included 556 758 individuals (57% male) born in Israel and consecutively assessed by the draft board at age 17 years. Linkage to the Israeli Bureau of Statistics registry indicated that over 98% of the Jewish boys born during those years who had survived the first year of life appeared in the draft board registry. The proportion for girls was lower since orthodox women are not assessed by the draft board. There were 2026 individuals (0.36%; 77% of whom were male) who had a last-discharge diagnosis of schizophrenia. There were 439 individuals (0.08%; 59% of whom were male) who had a last-discharge diagnosis of nonpsychotic bipolar disorder, and 890 individuals (0.16%; 63% of whom were male) who had a last-discharge diagnosis of depression or anxiety disorder.

On assessment by the draft board, 555 326 of the 556 758 individuals had no obvious signs of psychotic illness and were not admitted to a psychiatric hospital any time before or within 1 year from the draft board assessment. Of the 555 326 individuals, 1856 (76% male) had a last-discharge diagnosis of schizophrenia, 416 (59% male) had a last-discharge diagnosis of nonpsychotic bipolar disorder, and 801 (64% male) had a last-discharge diagnosis of depression or anxiety disorder.

## OPERATIONALIZATION OF DISCREPANCY BETWEEN ACTUAL AND PREDICTED INTELLECTUAL PERFORMANCE

While prospective longitudinal follow-up from early childhood into adulthood is the best method to determine changes in intellectual performance, this is impractical because of the low incidence of schizophrenia. Hence, estimates of premorbid intelligence have been used routinely as a means of comparing current intellectual deficits with intellectual potential before the onset of the schizophrenic illness.<sup>19,25</sup> These estimates are based on the assumption that certain intellectual abilities are minimally or not at all affected by the schizophrenic illness and can therefore be used as a gauge for estimating declines in intellectual functions due to schizophrenia.<sup>26,27</sup> A frequently used measure of premorbid intellectual ability is the ability to read and spell single words, an ability that is almost always acquired at an early age. Several studies have demonstrated the validity of using reading and spelling tests as estimates of premorbid intellectual ability in patients with schizophrenia, demonstrating comparable performance on such measures between patients with schizophrenia and controls.<sup>21,28-30</sup> Jones et al<sup>2</sup> and Fuller et al<sup>10</sup> demonstrated that vocabulary and reading abilities were unimpaired and stable over time in future patients with schizophrenia.

Hence, current intelligence scores (at age 17 years) that are lower than reading or spelling scores are, therefore, interpreted as reflecting a decline in intelligence before age 17 years, whereas similar spelling or reading scores and intelligence scores would suggest a relatively stable premorbid intellectual course. Conceivably, comparing measures of current intellectual ability (at age 17 years) with measures of intellectual potential using measures that were all collected *before* the onset of the illness would allow for the estimation of putative premorbid intellectual change.

Indices of discrepancy between spelling, reading, and intelligence scores at age 17 years were applied using a regres-

sion approach. This method enabled us to avoid the psychometric artifacts inherent in raw difference scores, ie, the curvilinear relationship between difference scores and total scores for any 2 tests.<sup>31</sup> For this method to be valid, the pairs of tests being used should be fairly highly correlated.<sup>31</sup> The multiple correlation between the reading and spelling tests and the IQ scores in never-hospitalized individuals was  $r=0.68$  ( $P<.001$ ). For the cohort of never-hospitalized individuals, we regressed IQ scores at age 17 years on reading, vocabulary, and spelling ability scores using linear regression. The resulting regression model was applied to the entire cohort (hospitalized and never-hospitalized individuals). The residual score (observed score minus predicted score) reflects the degree to which an individual's actual score differs from the predicted score. Thus, when we refer to putative IQ change, we are actually referring to a discrepancy between actual IQ in comparison with expected IQ based on predicted score. Owing to the categorical nature of the IQ, reading, and spelling measures, the putative IQ change score (residual score) was limited to 108 values in never-hospitalized individuals. Although this is technically a categorical variable, it was analyzed as a continuous variable since it had a large range of values, and the maximum difference between 2 adjacent values of the putative score was 1. Furthermore, residual scores were normally distributed, and kurtosis and skewness values were close to 0.

## STATISTICAL ANALYSIS

Cox proportional hazards regression models were used to examine the association of IQ change and subsequent risk of schizophrenia. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. The  $P$  values were computed using Wald  $\chi^2$ , and the significance level was set at .05 (2-sided). The proportional hazard assumptions were tested by examination of Nelson-Aalen cumulative hazard function plots and investigation of Schoenfeld residual plots.

First, we directly compared the number of individuals with extreme IQ change scores between future patients and never-hospitalized individuals. For this analysis, the residual scores (IQ change score) from the linear regression of IQ scores at age 17 years on reading and spelling ability scores were divided into 3 categories corresponding to the 95% CI and the bottom and top 2.5% of the residual-score distribution in the never-hospitalized individuals. The IQ change was then examined as a continuous measure and as a categorical measure to allow for a nonlinear effect of IQ changes on risk of schizophrenia. The IQ change score was divided into 6 categories corresponding to the following cut-off scores: actual IQ more than 20 points lower than expected IQ; actual IQ more than 10 and up to 20 points lower than expected IQ; actual IQ more than 0 and up to 10 points lower than expected IQ; actual IQ 0 to up to 10 points higher than expected IQ; actual IQ 10 to up to 20 points higher than expected IQ; and actual IQ more than 20 points higher than expected IQ. This scheme afforded natural groupings by IQ change scores. Results for IQ change analyzed as a continuous measure are presented in terms of discrepancies of 10-point increments between expected and observed IQ for ease of interpretation. The nonlinear relationship between IQ change and risk of schizophrenia was investigated by inclusion of a quadratic term in the models.

First, we fitted IQ change as the only predictor of schizophrenia. Subsequent models were adjusted for potential confounders and mediators. When adjusted models were conducted, variables were consistently defined, ie, all of the variables were treated as categorical or continuous in any regression model. Because a group with declines in IQ would also be more likely to have relatively low IQs, to ensure that the results are not ac-

counted for simply by low IQ scores at age 17 years,<sup>2,3</sup> we controlled for low (<85) actual IQ at age 17 years. We also controlled for the presence of nonpsychotic psychiatric diagnosis in adolescence,<sup>32,33</sup> sex,<sup>34</sup> and socioeconomic status (SES).<sup>35</sup> The SES was based on Israeli National Bureau of Statistics classification of geographical units by socioeconomic level. The first adjusted model included sex, SES, IQ, and nonpsychotic psychiatric diagnosis in adolescence. A second adjusted regression model also controlled for social functioning.<sup>4,21,36</sup> Since the draft board assesses social functioning only in male individuals, this adjusted model was restricted to male individuals and did not include sex.

Repeated-measures analysis of covariance models were used to assess change in raw, rather than residual, IQ scores. The within-subjects factor was the IQ measure (estimated and actual). The IQ measures (mean reading and spelling scores and actual IQ) were standardized. Diagnostic group was the between-subject factor. Covariates were as described earlier, but they did not include actual IQ. For effects involving the within-subjects factor, the F test was based on the Huynh-Feldt adjustment for the degrees of freedom. The association between IQ change and age at first psychiatric hospitalization was examined using Pearson correlation. Analyses were repeated for the outcomes of bipolar disorder and depression or anxiety disorder. Since the cohort included large sibships and since siblings represent nonindependent observations, analyses were also conducted after randomly selecting only 1 sibling per family.

## RESULTS

### DISTRIBUTION OF IQ CHANGE SCORE IN NEVER-HOSPITALIZED INDIVIDUALS AND FUTURE PATIENTS

Cox regression analysis demonstrated a significant difference between future patients with schizophrenia and never-hospitalized individuals in the proportion of individuals outside of the 95% CI ( $\chi^2=215.67$ ;  $P<.001$ ). Specifically, 8.2% of the future patients were in the bottom 2.5% of the residual-score distribution, 89.4% were within the 95% CI, and 2.4% were in the top 2.5% of the distribution. This indicates that the proportion of individuals with IQ scores much higher than expected at age 17 years was similar in future patients and never-hospitalized individuals. Future patients were represented more frequently among individuals with IQ scores that were much lower than expected.

### IQ CHANGE SCORE ANALYZED AS A CONTINUOUS VARIABLE

A significant association between IQ change score and risk for schizophrenia was found (HR=1.04; 95% CI, 1.03-1.05;  $\chi^2=414.18$ ;  $P<.001$ ). Thus, the lower the actual IQ was as compared with the expected IQ, the higher the risk was for schizophrenia. The change in the HR associated with each discrepancy of 10 IQ points was 1.48 (95% CI, 1.42-1.53;  $\chi^2=408.89$ ;  $P<.001$ ). In the analysis that adjusted for SES, low actual IQ, sex, and nonpsychotic psychiatric disorders in adolescence, and in the analysis that also adjusted for adolescent social withdrawal for male individuals, the adjusted HRs associated with each discrepancy of 10 IQ points were 1.33 (95% CI, 1.27-1.39;  $\chi^2=159.65$ ;  $P<.001$ ) and 1.40 (95% CI, 1.32-1.47;

$\chi^2=147.57$ ;  $P<.001$ ), respectively, indicating more than 30% higher risk for schizophrenia in individuals who had actual IQ scores that were 10 points lower than expected, holding SES, low actual IQ, sex, nonpsychotic psychiatric disorders in adolescence, and, for male individuals, adolescent social withdrawal constant.

### IQ CHANGE SCORE ANALYZED AS A CATEGORICAL VARIABLE

Having demonstrated a positive association between schizophrenia and IQ change score on a continuous scale, we then examined the effect of IQ change score on risk for schizophrenia using the aforementioned categories of 10-point discrepancies in IQ. The adjusted and unadjusted HRs for each of these categories relative to the group that had an increase of 0 to 10 points in IQ are presented in **Table 1**. The HRs in Table 1 suggest a non-linear relationship between IQ change and risk of schizophrenia, with individuals with largely lower-than-expected actual IQs having a greater risk than one would expect from a linear relationship. This was supported by a significant deviation from linearity in the unadjusted and adjusted models ( $\chi^2=11.48$ ,  $P<.001$ ;  $\chi^2=4.15$ ,  $P=.04$ ;  $\chi^2=4.72$ ,  $P=.03$  for the quadratic term in the unadjusted, first adjusted, and second adjusted models, respectively). Specifically, only individuals with lower-than-expected actual IQs were at a significantly increased risk of schizophrenia. There was no evidence for a modifying effect of low IQ (<85) on the association between IQ change score and risk for schizophrenia (all  $P>.50$  for the actual IQ by IQ change interaction).

It may be argued that the association between intellectual decline and schizophrenia is owing to a subgroup of future patients who were impaired on the language measures and thus probably already had impaired brain functions at a young age. Although such a group is likely to bias results toward the null, ie, underestimate the true association between IQ decline and schizophrenia, we assessed the interaction between language functioning and IQ decline. There was no significant interaction between the mean of the reading and spelling scores and the IQ change score ( $\chi^2=0.44$ ;  $P=.51$ ). Stratifying analyses based on normal language abilities (ie, individuals with intact acquisition of reading and spelling abilities defined as a percentile greater than 16 on the mean of the reading and spelling scores) and abnormal language abilities gave similar results, a comparable association between IQ change score and risk for schizophrenia in both groups (HR=1.03, 95% CI, 1.02-1.04; HR=1.04, 95% CI, 1.03-1.05; for normal and abnormal language groups, respectively).

### ANALYSIS BASED ON RAW SCORES

We also conducted analyses based on raw scores rather than residualized scores. **Table 2** shows the raw standardized reading and spelling ability (ie, expected IQ) and actual IQ scores of never-hospitalized individuals and of individuals later hospitalized for schizophrenia. Repeated-measures analysis of covariance models demonstrated significant effects of diagnosis, IQ measure, and

**Table 1. Effects of IQ Change Score Groups on the Prevalence of Schizophrenia in the Study Cohort\***

IQ Point Discrepancy	Cohort Size, No.†	Schizophrenia Cases, No.	Rate‡	HR (95% CI)		
				Unadjusted Model	Adjusted Model 1§	Adjusted Model 2¶
Actual IQ >20 points higher than expected IQ	48 129	79	16:10 000	0.65 (0.51-0.83)	0.66 (0.52-0.85)	0.68 (0.52-0.90)
Actual IQ from 10 to ≤20 points higher than expected IQ	83 545	146	17:10 000	0.69 (0.58-0.85)	0.72 (0.59-0.87)	0.62 (0.49-0.78)
Actual IQ from 0 to ≤10 points higher than expected IQ	141 539	354	25:10 000	1.00	1.00	1.00
Actual IQ >0 and ≤10 points lower than expected IQ	152 830	526	34:10 000	1.36 (1.19-1.56)	1.26 (1.10-1.44)	1.23 (1.05-1.44)
Actual IQ >10 and ≤20 points lower than expected IQ	89 928	460	51:10 000	2.00 (1.74-2.30)	1.70 (1.46-1.96)	1.83 (1.54-2.17)
Actual IQ >20 points lower than expected IQ	33 495	291	86:10 000	3.38 (2.89-3.95)	2.27 (1.89-2.71)	2.54 (2.05-3.15)

Abbreviations: CI, confidence interval; HR, hazard ratio.

\*The IQ change score groups are based on residualized scores.

†Cohort refers to never-hospitalized individuals.

‡Rate is expressed as number of schizophrenia cases per number of individuals in cohort.

§Model 1 adjusted for sex, socioeconomic status, low IQ, and nonpsychotic psychiatric disorders at the time of the draft board assessment; model 2 adjusted for socioeconomic status, low IQ, social withdrawal, and nonpsychotic psychiatric disorders at the time of the draft board assessment.

||Reference category.

a significant measure × diagnosis interaction (**Table 3**). Analyses of covariance showed statistically significant IQ deficits in the schizophrenia group as compared with never-hospitalized individuals for both IQ scores (all  $F > 50.00$ ; all  $P < .001$ ). However, using the criteria by Cohen,<sup>37</sup> the effect size for the estimated IQ was less than small, and it was possibly clinically nonsignificant. The interaction was accounted for by the significantly larger difference between actual and expected premorbid IQs in future patients ( $P < .05$  with Bonferroni adjustment).

### COURSE OF PREMORBID INTELLECTUAL CHANGE

Patients were assigned to 1 of 3 groups in accordance with the classification used in previous studies.<sup>9,38</sup> The stable good group (“preserved”) included patients with normal actual IQ ( $\geq 85$ ) who demonstrated a decline of less than 10 points as evidenced by the difference between actual and expected IQ scores. The stable poor group (“compromised”) included patients with poor actual IQ ( $< 85$ ) that was also expected to be poor (change of less than 10 points). The “deteriorated” group included patients who displayed a decline of 10 or more IQ points as evidenced by the difference between actual and expected IQ regardless of actual IQ score. Descriptive analysis demonstrated that 51% of future patients with schizophrenia were preserved, 9% were compromised, and 40% were deteriorated. Further analyses showed that whereas 23% of future patients with schizophrenia with normal actual IQ scores had deteriorated, 75% of future patients with schizophrenia with poor actual IQ scores had deteriorated (**Table 4**).

There was no significant association between IQ change and age at first psychiatric admission with schizophrenia ( $P = .87$ ). We tested the association between IQ change and other major psychiatric diagnoses. No significant association was found between IQ change

**Table 2. Estimated and Actual Standardized IQ Scores**

Population	Standardized Score*
Cohort†	
Estimated IQ	0.00
Actual IQ	0.00
Schizophrenia cases	
Estimated IQ	-0.18
Actual IQ	-0.49

\*Marginal means were similar for model 1 (which adjusted for sex, socioeconomic status, and nonpsychotic psychiatric disorders at the time of the draft board assessment) and model 2 (which adjusted for socioeconomic status, social withdrawal, and nonpsychotic psychiatric disorders at the time of the draft board assessment). The higher scores are presented.

†Cohort refers to never-hospitalized individuals.

**Table 3. Group Comparisons of Estimated and Actual Standardized IQ Scores\***

Main Effect	Model 1		Model 2	
	$F_{1, 551 317}$	<i>P</i> Value	$F_{1, 289 456}$	<i>P</i> Value
Diagnosis	299.04	<.001	178.22	<.001
Measure	16.40	<.001	467.41	<.001
Interaction	238.44	<.001	200.65	<.001

\*Model 1 adjusted for sex, socioeconomic status, and nonpsychotic psychiatric disorders at the time of the draft board assessment; model 2 adjusted for socioeconomic status, social withdrawal, and nonpsychotic psychiatric disorders at the time of the draft board assessment.

and risk of hospitalization with nonpsychotic bipolar disorder or with depression or anxiety disorder, thus supporting the specificity of the earlier association with schizophrenia. Similar results were obtained when analyses were restricted to only 1 randomly selected member per family, and the results are therefore described only for the larger cohort.

**Table 4. Intellectual Status and Course of Premorbid Intellectual Functioning at Age 17 Years**

	Individuals With IQ Within Normal Range ( $\geq 85$ ), No. (%)	Individuals With Low IQ ( $< 85$ ), No. (%)
Future cases	1240 (67)	616 (33)
Course*		
Stable	950 (77)	155 (25)
Deteriorating	290 (23)	461 (75)

\*Stable indicates a decline of less than 10 points as evidenced by the difference between actual and expected IQ scores; deteriorating indicates a decline of 10 or more IQ points as evidenced by the difference between actual and expected IQ scores.

#### COMMENT

The results of the present study suggest that before the onset of schizophrenic psychosis, some future patients exhibit a declining course in intellectual performance. Findings are independent of sex, SES, the presence of non-psychotic psychiatric disorders in adolescence, and adolescent social withdrawal. The current study extends previous findings of premorbid intellectual deficits in schizophrenia by further demonstrating that for a considerable proportion of future patients, lower-than-normal premorbid intellectual performance is likely to reflect processes occurring during childhood and adolescence. Almost three quarters of the future patients with schizophrenia who had low IQ at age 17 years had lower-than-expected IQs based on reading and spelling scores. In addition, lower-than-expected IQs were observed in approximately one quarter of future patients with schizophrenia with IQ within the normal range ( $\geq 85$ ) at late adolescence, and lower-than-expected IQs were associated with risk for schizophrenia in this group as well.

Lower-than-expected IQ may reflect either relative or absolute deterioration. A relative deterioration, or dysdevelopment, reflects a lack of appropriate development of intellectual functions as expected, for instance, based on age or education. Such a process is characterized, for example, by stability of the group mean score in patients coupled with improvement in never-hospitalized individuals over time, suggesting "failure to keep pace" (for a similar view, see Fish et al<sup>39</sup> and Bedwell et al<sup>40</sup>). If absolute deterioration occurs, a decline in the group mean score of patients should be observed. Both processes, however, will be characterized by projected decline in intellectual functioning (ie, patients having lower-than-expected performance based on regression scores more frequently than never-hospitalized individuals).

We found significant change over time in absolute scores coupled with projected declines. Therefore, we believe that the association observed in our study is not mirroring only a relative, dysdevelopmental process, but, for some future patients, an actual decline. This conclusion is supported by several lines of evidence. First, in the 1946 British birth cohort study, Jones et al<sup>2</sup> found that the difference in intellectual performance between future patients and controls widens between ages 8 to 15 years.

Other studies have also described absolute intellectual decline from childhood to adolescence before the onset of psychosis.<sup>9,10,12,41</sup> Kremen et al,<sup>8</sup> who studied the association between IQ at ages 4 and 7 years and later psychotic symptoms, found both absolute and projected decline. Finally, children who were exposed to rubella in utero and later developed psychosis had an IQ decline of 11 points from childhood to adolescence.<sup>42</sup> However, a definite interpretation is not possible owing to the cross-sectional design of the current study. A prospective longitudinal follow-up from early childhood into adulthood with multiple assessment points is needed to provide a more conclusive test of the hypothesis that absolute IQ decline predates psychosis.

It may be argued that differences between IQ scores and reading and spelling abilities could have existed early on instead of reflecting change over time. In a study of monozygotic twins, Goldberg et al<sup>43,44</sup> described a 1.5-point discrepancy between estimated premorbid IQ (based on reading scores) and current IQ in the unaffected cotwins of patients with schizophrenia. A larger discrepancy was observed in the affected twins. The discrepancy in healthy twin pairs was only about 0.5 points. However, the study by Jones et al,<sup>2</sup> which followed the British 1946 birth cohort over childhood and early adolescence, indicates that while a difference between language functions such as reading and vocabulary abilities and IQ may indeed exist in schizophrenia early on, it is of small magnitude during childhood and significantly widens from childhood to adolescence. Fuller et al<sup>10</sup> described similar findings.

The results described here are consistent with the neurodevelopmental hypothesis of schizophrenia. The early neurodevelopmental hypothesis<sup>45,46</sup> postulates that the etiological factors operate early (ie, prenatal or perinatal) in life, creating a static neurodevelopmental encephalopathy that lies relatively silent until the operation of brain maturational processes in adolescence. An alternative model suggested that abnormal development occurs later in life. This late neurodevelopmental hypothesis<sup>47</sup> suggests that if brain maturation in adolescence must be invoked, then perhaps it is abnormal rather than normal, and the crucial pathological processes might operate during this period. Woods<sup>48</sup> has suggested a progressive neural process that is continuous throughout childhood and adolescence.

Our findings support 3 possible courses of premorbid intellectual functioning in schizophrenia<sup>9,30,49</sup>: (1) those who start with IQ scores of 85 or higher as children and remain at the same level in adolescence (good and stable); (2) those who start with IQs below 85 and remain at this level (poor and stable); and (3) those whose IQ deteriorates from childhood to adolescence (deteriorating). Our findings suggest a further distinction within the deteriorating group between those patients remaining within the normal range vs those with impaired premorbid IQ. These courses may correspond to the different developmental trajectories in schizophrenia. For example, poor and stable IQ may represent the early developmental group; deteriorating to impaired IQ may represent the late developmental and/or progressive cases. The distinction between different courses is also supported by studies

showing a relationship between different courses of pre-morbid functioning and symptom severity.<sup>9,50,51</sup> Patients with deteriorating intellectual functions have been characterized as having more chronic symptoms and being more likely to be treatment nonresponders.<sup>51,52</sup>

Limitations of the current study should be noted. First, the possibility of bias owing to misclassification of cases should be considered. Although the overwhelming majority of individuals who receive a diagnosis of schizophrenia in the course of their lives will be hospitalized or will receive some form of hospital-based treatment at their first psychotic episode or shortly thereafter,<sup>53-55</sup> some individuals with schizophrenia are never hospitalized, and others are hospitalized later in life. Hence, most, but not all, individuals with schizophrenia are included in the NPHCR. This is, however, likely to bias results toward the null, ie, underestimate the true association between IQ decline and schizophrenia. Furthermore, the prevalence of schizophrenia in our cohort was 0.36%. Prevalence for cohort members with the longest follow-up (17 years since the draft board assessment) was 0.57%, which is similar to rates (0.61%-0.72%) published for cohorts followed until ages 40 to 46 years using similar ascertainment methods.<sup>2,56</sup> Hence, our study population probably includes a good representation of lifelong schizophrenia cases with hospitalization. Subjects in the cohort with psychiatric disorders other than schizophrenia are likely to be somewhat less representative of all such cases in the population since admission to the hospital is less invariable. Prevalence of nonpsychotic bipolar disorder was 0.08%, and prevalence of depression and anxiety disorders was 0.16%. Prevalences for cohort members with the longest follow-up were 0.11% and 0.24%, respectively, which are lower than rates from door-to-door interviews.<sup>5</sup> Therefore, the results for these groups should be interpreted with caution and are probably generalizable only to cases with severe forms of such disorders.

In conclusion, in a large, historical, population-based cohort study, we demonstrated that schizophrenia is associated with pre-morbid intellectual decline. However, it is not yet clear whether this is a causal risk factor. Therefore, a parsimonious explanation may be that decline in IQ during adolescence reflects neurobiological processes intrinsic to the development of psychotic symptoms.

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