

## Premorbid Neurocognitive Functioning in Schizophrenia Spectrum Disorder

Holger J. Sørensen<sup>2,3</sup>, Erik L. Mortensen<sup>1,2,4</sup>,  
Josef Parnas<sup>2,5</sup>, and Sarnoff A. Mednick<sup>2,6</sup>

<sup>2</sup>Danish Epidemiology Science Center, Institute of Preventive Medicine, Copenhagen University Hospital; <sup>3</sup>Department of Psychiatry, Copenhagen University Hospital, Amager, Copenhagen; <sup>4</sup>Department of Health Psychology, Institute of Public Health, University of Copenhagen; <sup>5</sup>Department of Psychiatry, Copenhagen University Hospital, Hvidovre, Copenhagen; <sup>6</sup>Social Science Research Center and Department of Psychology, University of Southern California, USA

**A prospective study based on the U.S. National Collaborative Perinatal Project and using the Wechsler Intelligence Scale for Children (WISC) found lower test scores for the Coding subtest in preschizophrenic children than in their unaffected siblings. Using data on cognitive functioning in adolescence, the aim of the present prospective study was to examine whether low scores on Coding is associated with the risk of developing schizophrenia spectrum disorders. The 12 subtests of the WISC were administered to 311 children and adolescents with a mean age of 15.1 years (range: 8 to 20 years), and the diagnostic assessment (DSM-III-R) was conducted by senior clinicians 25 years later. The group with schizophrenia spectrum disorder consisted of 84 individuals, and this group obtained significantly lower scores on Coding than nonschizophrenic controls. This difference could not be explained by differences in WISC IQ. Logistic regression analysis controlling for age at examination, gender, and social status yielded a significant, but relatively weak, association between low Coding test score and risk of schizophrenia spectrum disorder. For each unit increase in the Coding raw score, the adjusted odds ratio was 0.97 (95% CI 0.94–1.00) ( $p = .022$ ), and the risk of schizophrenia spectrum disorder decreased by 3% (95% CI 6 to 0%). The Coding deficit on the WISC may indicate deficits in perceptual motor speed or in working memory processing speed in young individuals who later develop schizophrenia, schizotypal personality disorder, or other disorders within the schizophrenia spectrum.**

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<sup>1</sup>To whom correspondence should be addressed; e-mail: e.l.mortensen@pubhealth.ku.dk.

### Introduction

Schizophrenia is often considered a neurodevelopmental disorder,<sup>1</sup> and findings from follow-up studies have supported a relationship between cognitive impairment in childhood and risk of schizophrenia later in life.<sup>2–4</sup> Two large epidemiological studies of male draftees also demonstrated a strong relationship between low IQ and subsequent risk of hospitalization with schizophrenia and other psychosis.<sup>5–6</sup> However, in other prospective studies of individuals at high risk for schizophrenia, a significant relationship between low premorbid IQ and risk of later schizophrenia could not be confirmed.<sup>7–8</sup>

For the Wechsler scales, it is also not firmly established whether Total IQ or specific subtests have the strongest association with later schizophrenia.<sup>9</sup> So far, only a few prospective studies have shed light on this question. A trend toward lower Performance IQ among prepsychotic individuals was reported in the New York High-Risk Project.<sup>10</sup> In an analysis based on the U.S. National Collaborative Perinatal Project, Niendam et al.<sup>11</sup> evaluated childhood cognitive functioning in individuals who later developed schizophrenia and in their unaffected siblings. Preschizophrenic children and their unaffected siblings had lower scores for Picture Arrangement, Vocabulary, and Coding than comparison subjects but differed from each other only on the Coding subtest. Based on these findings, it was suggested that children who later develop schizophrenia exhibit more severe deficits in perceptual-motor speed and in speeded processes of working memory than their unaffected siblings.

Studies of individuals at genetic high risk for schizophrenia may contribute by examining whether some subtests have a stronger association with later schizophrenia than others. The Copenhagen High-Risk Study consists of 311 participants who have been followed since 1962.<sup>12</sup> Three assessments were conducted: an assessment at a mean age of 15 years, an assessment at a mean age of 22 years, and a diagnostic follow-up at a mean age of 39 years. A previous report did not suggest differences in mean total IQ in preschizophrenic subjects as opposed to controls.<sup>13</sup> This report did not examine whether any of the 12 IQ subtests at a mean age of 15 years predicted later schizophrenia. A recent study of the course of general cognitive functioning in high-risk individuals with psychosis outcomes found support for the hypothesis

that general intelligence scores would decline over time in patients with psychosis compared with healthy individuals and adults with other mental disorders.<sup>14</sup> The current study made use of archival data from this longitudinal sample to examine premorbid scores on IQ subtests in schizophrenia and related disorders (the data obtained at the second assessment at a mean age of 22 years were not included in the present study).

Comparison of the findings of the National Collaborative Perinatal Project and those of an independent sample composed of individuals at genetic high risk for schizophrenia may illuminate the hypothesis that preschizophrenic adolescents exhibit deficits in aspects of working memory. Given a premorbid disturbance in speeded processes of working memory, deficits would be expected not only in Coding but also in Digit Span and Arithmetic. The Copenhagen High-Risk Study spans a 25-year follow-up period. A relatively high number of cases with both Axis I (psychotic) disorders and Axis II disorders (schizotypal personality disorder, or SPD) in the schizophrenia spectrum have been identified in this sample, which enables us to examine premorbid IQ in psychotic, as well as nonpsychotic disorders (SPD), within that spectrum. Schizophrenia shares some features with schizotypal personality, and a biological relationship between schizophrenia and schizotypal personality disorder has been supported in genetic and family studies.<sup>15</sup> A study of patients with SPD suggests significant deficits on measures of verbal learning and abstraction and mild general impairment in other cognitive domains, a profile similar to that found in subjects with schizophrenia, albeit less severe.<sup>16</sup> Another study suggests a mild to moderate general impairment of cognitive performance and proportionally greater involvement of verbal measures of persistence, short-term retention, and learning in subjects with schizotypal personality disorder.<sup>17</sup> It is uncertain, however, whether “preschizophrenics” display more severe premorbid neuropsychological deficits than “preschizotypals.”

## Methods

The Copenhagen High-Risk Study consists of 311 participants who have been followed since 1962. Of this cohort, 207 members were offspring of mothers who had been diagnosed with schizophrenia. These individuals were matched to 104 low-risk individuals on a variety of variables, including age and social status.<sup>12</sup> The Wechsler Intelligence Scale for Children (WISC) consists of 12 subtests: Arithmetic, Information, Comprehension, Similarities, Vocabulary, Digit Span, Picture Comprehension, Picture Arrangement, Block Design, Object Assembly, Coding, and Mazes.<sup>18</sup> Participants were administered all tests at the mean age of 15.1 years (range: 8 to 20 years). None had a psychiatric diagnosis at the time. Two major interview-based diagnostic follow-ups have been conducted since 1962, as described in detail

elsewhere.<sup>19</sup> The second diagnostic follow-up was conducted between 1986 and 1989. Individuals (and their hospital records) were thoroughly assessed with a number of diagnostic tools and rating scales, and each person was assigned a primary lifetime diagnosis representing the most severe Axis I or II diagnosis at either assessment using DSM-III-R criteria.<sup>19</sup>

After the second diagnostic follow-up, 8 cases with schizophrenia spectrum disorder (7.7%) were found among low-risk individuals, and 76 cases (36.7%) with schizophrenia spectrum disorder were found among high-risk individuals. An association of high-risk status with low IQ has already been documented in this sample.<sup>12</sup> However, the largest proportion of high-risk individuals did not develop a schizophrenia spectrum disorder. Given prior knowledge of the association of high-risk status with low offspring IQ and the strong association of high-risk status on offspring risk of the disorder, the relationship between IQ and risk of schizophrenia spectrum disorder may be modified by high-risk status. Consequently, we decided not only to focus on the potential associations between childhood IQ subtest performance and diagnostic outcome but also to examine the influence of high-risk status on the association between IQ and diagnostic outcome. This was done by stratification of the sample according to genetic risk status.

## Data Analysis

We used the primary lifetime diagnosis representing the most severe Axis I or II diagnosis after the second follow-up. At that time cohort members averaged 39 to 42 years of age. Of the 311 individuals, 127 (40.8%) were confirmed to have no psychiatric diagnosis on Axis I or Axis II. A total of 84 (27.0%) had received a diagnosis within the schizophrenia spectrum: 43 (13.8%) had received a diagnosis of either schizophrenia, schizoaffective disorder, schizophreniform disorder, or atypical psychosis, and 41 (13.2%) had received a diagnosis of schizotypal personality disorder.<sup>19</sup> Of the remaining 100 individuals, 81 were confirmed to have a nonschizophrenic lifetime psychiatric diagnosis, while 19 who did not participate in the follow-up were excluded.

We examined the mean scores of Total IQ and the 12 IQ subtests with respect to diagnostic outcome categories using independent samples *t*-tests. Cohen's *d* was used to estimate effect size. Statistical significance was set at  $p < .05$ .

## Results

Table 1 compares Axis I schizophrenia spectrum disorders (“prepsychotic”) and the group with Axis II schizophrenia spectrum disorders (“preschizotypals,” or pre-SPD) with respect to Total IQ and the 12 WISC subtests. The pre-SPD group displayed significantly lower mean scores on Digit Span and Block Design

**Table 1.** The Mean Total IQ and the 12 Subtests of the Wechsler Intelligence Scale for Children (WISC) (at the Mean Age of 15.1 Years) in Relation to Psychiatric Outcome Status 25 Years Later

	Axis I SZ (n = 43)	Axis II SPD (n = 41)	No Diagnosis (n = 127)	Axis I SZ vs. Axis II SPD (df = 82)	Axis I SZ vs. No Diagnosis (df = 168)	Axis II SPD vs. No Diagnosis (df = 166)
Total IQ	101.7	101.5	103.4	NS	NS	NS
Arithmetic	11.4	11.4	11.9	NS	NS	NS
Comprehension	13.3	14.8	14.7	NS	NS	NS
Digit Span	10.2	9.5	9.8	0.03	NS	NS
Information	18.1	18.4	18.4	NS	NS	NS
Similarities	14.1	14.4	14.4	NS	NS	NS
Vocabulary	49.6	48.7	50.9	NS	NS	NS
Block Design	35.4	30.5	34.6	0.05	NS	0.06
Coding	46.2	45.4	51.2	NS	0.02	0.005
Mazes	16.5	16.2	16.1	NS	NS	NS
Object Assembly	25.5	23.3	25.6	0.04	NS	0.005
Picture Arrangement	29.5	29.9	30.7	NS	NS	NS
Picture Comprehension	13.5	13.1	13.1	NS	NS	NS

*Note:* The outcomes are Axis I (psychotic) schizophrenia spectrum disorder (SZ), Axis II schizophrenia spectrum disorder (SPD), and no psychiatric diagnosis. The *p*-values refer to independent samples *t*-tests of mean differences between diagnostic categories.

as compared with the prepsychotic group. The mean scores on total IQ and the 10 remaining IQ subtests did not differ significantly between the 2 groups. The table also shows that, compared with healthy controls, both prepsychotic and pre-SPD individuals had a significantly lower mean raw score on Coding. Additionally, the pre-SPD group had significantly lower mean scores with respect to Object Assembly and a trend ( $p = .06$ ) in the same direction for Block Design.

We increased the sample size for analysis by collapsing the prepsychotic and pre-SPD groups into 1 group with schizophrenia spectrum disorder ( $n = 84$ ). Subsequent analyses compared the schizophrenia spectrum group with the no diagnosis group ( $n = 127$ ) and with the cohort members ( $n = 81$ ) with other psychiatric diagnoses (psychiatric controls). We observed significantly lower mean scores on Coding in the spectrum group than among healthy controls ( $p = .001$ ), and a weaker, albeit significant, difference on Coding was also observed when we compared the preschizophrenia spectrum group with psychiatric controls ( $p = .05$ ). No other significant group differences were observed (Table 2).

Subsequent analysis of covariance (ANCOVA) with adjustment for age at the time of IQ testing (entered as a continuous variable) yielded virtually the same results as those presented in Table 1 and Table 2 (data not shown). Seventy-five of the cohort members (24%) were above 16 years old when they were examined with the WISC in 1962. However, restricting the cohort to individuals who were 16 years or younger in 1962

showed virtually the same results as those presented in tables.

ANCOVA with adjustment for age and including gender as a categorical factor indicated no significant interaction between gender and follow-up psychiatric outcome for any test score (data not shown). Adjustment for age, gender, and social status (0–6 point scale from low to high status) showed that the schizophrenia spectrum group performed worse than the healthy controls at  $p = .01$  and worse than psychiatric controls at  $p = .02$ .

The unadjusted mean Coding raw score of the 104 individuals at genetic low risk was 52.0, and the unadjusted mean Coding raw score of individuals at genetic high risk was 48.2 (high-risk versus low-risk comparison:  $p = .02$ ; effect size = 0.28). However, the interaction between history of maternal schizophrenia (high-risk versus low-risk status) and follow-up psychiatric outcome was not significant. Within the low-risk subsample, 8 cases with schizophrenia spectrum disorder were found (7.7%), and these 8 cases obtained a mean Coding score of 43.6, while the healthy controls ( $n = 59$ ) obtained a mean score of 52.6 ( $p = .05$ ; effect size = 0.73). Within the high-risk subsample of 207 individuals, 76 cases with schizophrenia spectrum disorder were found (36.7%). The mean Coding raw score for these cases was 46.0, while the mean for the healthy controls ( $n = 68$ ) was 50.0 ( $p = .10$ ; effect size = 0.28).

To evaluate the extent to which a low test score on Coding predicted later schizophrenia spectrum disorder we used multiple logistic regression analysis with

**Table 2.** The Mean Total IQ and the 12 Subtests of the Wechsler Intelligence Scale for Children (WISC) (at the Mean Age of 15.1 Years) in Relation to Psychiatric Outcome Status 25 Years Later

	SZ-Spectrum (n = 84)	No Diagnosis (n = 127)	Psychiatric Controls (n = 81)	SZ-Spectrum vs. No Diagnosis ( <i>df</i> = 209)	SZ-Spectrum vs. Normal Controls Effect Size	SZ-Spectrum vs. Psychiatric Controls ( <i>df</i> = 163)	SZ-Spectrum vs. Psychiatric Controls Effect Size
Total IQ	101.6	103.4	100.68	NS	0.14	NS	0.06
Arithmetic	11.4	11.9	11.4	NS	0.22	NS	0.001
Comprehension	14.0	14.7	14.0	NS	0.12	NS	0.001
Digit Span	9.9	9.8	9.7	NS	0.04	NS	0.09
Information	18.3	18.4	17.1	NS	0.04	NS	0.22
Similarities	14.3	14.4	14.0	NS	0.03	NS	0.07
Vocabulary	49.2	50.9	48.6	NS	0.12	NS	0.04
Block Design	33.1	34.6	33.3	NS	0.13	NS	0.02
Coding	45.8	51.2	50.3	0.001	0.41	0.05	0.30
Mazes	16.4	16.2	16.0	NS	0.09	NS	0.12
Object Assembly	24.5	25.6	24.7	0.10	0.27	NS	0.07
Picture Arrangement	29.7	30.7	30.4	NS	0.14	NS	0.10
Picture Comprehension	13.3	13.1	13.2	NS	0.04	NS	0.003

Note: The *p*-values refer to independent samples *t*-tests of mean differences between diagnostic categories.

schizophrenia spectrum disorder versus control status as the outcome. The initial analysis showed that the Coding raw score predicted the outcome ( $p = .004$ ). When age (years) at time of IQ testing and gender were included as covariates, the Coding score remained a significant predictor of the outcome ( $p = .011$ ). For each unit increase in the Coding raw score, the adjusted odds ratio was 0.97 (95% CI 0.94–0.99) ( $p = .011$ ). We further adjusted for social status as a continuous variable and found that the predictive capacity of Coding in relation to the outcome remained statistically significant ( $p = .022$ ). With social status included in the model, the adjusted odds ratio associated with one unit increase in the Coding raw score was 0.97 (95% CI 0.94–1.00). This implies that for each unit increase in the raw test score, the risk of schizophrenia spectrum disorder decreased by 3% (95% CI 6 to 0%).

## Discussion

We observed an association between premorbid low test scores on Coding and risk of subsequently developing schizophrenia spectrum disorder. Future patients with schizophrenia spectrum disorder obtained lower scores on Coding than individuals with no psychiatric diagnosis and the total cohort pool of nonschizophrenic controls. Low IQ did not predict schizophrenia or schizophrenia spectrum disorder, and the observed Coding deficit in schizophrenia spectrum disorder could not be explained by group differences with respect to IQ or by potential

confounding factors such as age at testing, gender, or social status. Coding score was significantly associated with genetic risk status (high-risk individuals had a lower mean score than low-risk controls), but a nonsignificant trend indicating lower mean scores on Coding in those who went on to develop schizophrenia spectrum disorder was observed both in the high-risk and low-risk subgroups (these findings should be interpreted in the light of limited statistical power, especially in the low-risk stratum).

Both our results and findings from the National Collaborative Perinatal Project<sup>11</sup> suggest an association between low Coding score and risk of schizophrenia or related disorders. The sample characteristics of the Copenhagen High-Risk Study differ considerably from the National Collaborative Perinatal Project, and it is remarkable that both studies showed that future patients with schizophrenic (or with schizophrenia spectrum) disorder performed worse than nonschizophrenic control groups on the Coding subtest. Despite differences in sample characteristics, both studies were able to control for several factors, including social status, that might otherwise confound the results. Poor performance on Coding has also been observed in high-risk adolescents,<sup>12,15</sup> in patients with schizophrenia,<sup>16</sup> including schizophrenia with childhood onset.<sup>20</sup> We were able to compare the Coding score of the schizophrenia spectrum group with a psychiatric control group and found some specificity of the association between low test scores on the Coding subtest and schizophrenia spectrum outcome. However, we did not examine in detail the specificity of the

association between premorbid cognition and a broader range of adult psychiatric disorders. Childhood disorders such as Attention Deficit Hyperactivity Disorder (ADHD) may display Coding deficits and may also show continuity with adult psychiatric disorders. The observed Coding deficits may have been mediated through disorders such as ADHD, but a recent study investigating cognitive functioning of children and adolescents found lower Coding scores in the schizophrenia spectrum group than in a comparison group consisting of children with ADHD.<sup>20</sup>

Niendam et al. suggest that the poor performance of future patients with schizophrenia on the Coding subtest may reflect a deficit in perceptual-motor speed and speeded processes of working memory.<sup>11</sup> However, the Coding subtest is a multidimensional task that assesses a complex array of cognitive functions, and in addition to working memory, good performance assumes attention, concentration, and psychomotor speed, including motor agility. In the National Collaborative Perinatal Project, preschizophrenic individuals also had reduced scores on Picture Arrangement, and the authors suggest a possible underlying deficit in mental sequencing or an underlying disturbance in social cognition. The authors interpret reduced scores on the Vocabulary subtest at age 7 as suggestive of a possible underlying focal deficit in language acquisition.<sup>11</sup> We did observe lower scores on Picture Arrangement and Vocabulary in the spectrum group, but the differences between this group and the controls were not significant. This discrepancy may be related to sample selection factors, age of testing, and time between testing and first signs of the disease.

We also observed that the risk of subsequently developing schizophrenia spectrum disorder was unrelated to the 11 other WISC subtests and that there was almost no premorbid difference between the Axis I (psychotic) schizophrenia spectrum and the SPD groups on the 12 WISC subtests. Another study observed similar neuropsychological deficits in patients with schizophrenia and patients with SPD, (albeit less severe in SPD),<sup>16</sup> and antecedent cognitive abnormalities may be part of both syndromes. However, a somewhat more impaired neuropsychological profile was anticipated in subjects who later developed Axis I (psychotic) schizophrenia spectrum disorder. Therefore, the finding that “preschizotypals” performed significantly worse than “prepsychotic” individuals on Digit Span, Block Design, and Object Assembly was unexpected and requires further study. This finding should be seen in the light of the growing literature indicating that, compared with healthy controls, people with lifetime psychosis diagnoses show deterioration in general cognitive functioning.<sup>2,4,21</sup> Recent findings from the Copenhagen High-Risk Study suggest that in high-risk individuals with psychosis outcome, general intelligence declines over time.<sup>14</sup> In contrast, cognitive impairment may reflect stable developmental traits in individuals who develop SPD in adulthood.

The finding (Table 1) that “prepsychotic” individuals did quite well on the Digit Span subtest is surprising since studies of adult patients with schizophrenia suggest impairment on this task.<sup>22</sup> The forward Digit Span task was employed in the current study, and the forward task probably makes less demand on working memory than the backward Digit Span. Thus, it has been shown that patients with schizophrenia show a less extensive pattern of correlation with attention, visual retention, executive functions, and motor functions on the forward Digit Span than on the backward digit span,<sup>23</sup> and it has also been found that nonpsychotic relatives of patients with schizophrenia show deficits on the backward Digit Span but not the forward Digit Span subtest.<sup>24</sup>

In conclusion, the present findings indicate a weak to moderate capacity of the Coding subtest to predict future schizophrenia spectrum disorder when it was administered to young individuals at a mean age of 15 years. For each unit increase in the raw test score on the Coding subtest, the risk of schizophrenia spectrum disorder decreased by 3% (95% CI 6 to 0%). However, the risk of subsequently developing schizophrenia spectrum disorder was unrelated to the 11 other WISC subtests, and few premorbid differences were observed between the adolescents who later developed Axis I (psychotic) schizophrenia spectrum disorders and those who developed schizotypal personality disorder. Therefore, additional work is needed to examine whether premorbid low test scores on Coding are associated with particular clinical dimensions within the schizophrenia spectrum disorders.

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