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Secondary Prevention of Schizophrenia: Utility of Standardized Scholastic Tests in Early Identification

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Background. *Given the enormous societal burden of schizophrenia, there has been a growing interest in its prevention during the past decade. Early detection and prompt treatment may improve outcome in schizophrenia. In this study, we examine the value of using pre-morbid cognitive impairment in early detection.*

Methods. *Standardized achievement tests Iowa Test of Basic Skills (ITBS) and Iowa Tests of Educational Development (ITED) at Grades 4, 8 and 11 were examined in 70 patients with schizophrenia and 147 comparison subjects without schizophrenia. The majority of comparison subjects later developed another major mental illness such as substance abuse or mood disorder. Receiver operating characteristic curves were used to test the efficiency and accuracy of pre-morbid cognitive tests for differentiating adolescents who will later develop schizophrenia from those who remain well or develop another mental illness.*

Results. *Although schizophrenia patients had lower mean percentile ranks than comparison subjects in every ITBS/ITED sub-test, these differences were only associated with small increases in risk for schizophrenia. Standardized scholastic tests achieved moderate sensitivity and specificity, and enhanced the detection of schizophrenia by three to five fold. However, positive predictive values were low. ITBS/ITED scores alone cannot be used in screening the general population, given the low positive predictive values.*

Conclusion. *Combining ITBS/ITED scores with other risk factors, such as family history, may lead to more efficient early detection. Our findings illustrate the challenges facing the secondary prevention of schizophrenia. Priority should be given to developing efficient and accurate methods of early detection in order to reduce the dangers of making erroneous false positive diagnoses, and to decrease exposure to unnecessary treatment during the testing of early interventions.*

Keywords Schizophrenia, Cognition, Premorbid, Prevention, Risk factors, Predictive value of tests, Longitudinal study

INTRODUCTION

Researchers and clinicians are increasingly aware that many patients with schizophrenia go untreated for extended periods of time before they eventually begin psychiatric treatment. The Northwick Park Study was among the first to report this alarmingly lengthy treatment delay (1). This finding has since been replicated in multiple first-episode studies (2–14). Increased awareness of long durations of untreated initial psychosis, together with recognition that secondary prevention may be critical in improving outcome of schizophrenia, have led to a proliferation of early intervention programs during the past decade.

Many of these early intervention programs share three common characteristics. Like the pioneering EPPIC and PACE programs from Australia (9,15,16), most of them sport catchy acronyms (e.g. TIPS, RAP, PRIME, PEPP). These names have been carefully chosen in an attempt to reduce the stigma of

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mental illness, and to help attract the older adolescents and young adults they serve. These programs also aim to provide prompt initial assessments and deliver comprehensive, integrated clinical care—an improvement over the fragmented services that patients with more established psychotic disorders often receive (17,18).

Another characteristic that these programs share is the approach to early identification, which was pioneered by Falloon (19) and further refined by McGorry (9,15,16). A system of multiple referral sources is established through networking with community mental health workers, primary care physicians, and school officials, and through carefully targeted educational activities to raise awareness, recognition and referral of people in the early phases of psychotic disorders. Although this approach combines state-risk factors (i.e. prodromal symptoms) with trait-risk factors (i.e. family and individual history), most patients have been identified based on the former (20).

Compared with pre-program historical controls, patients in the EPPIC and TIPS programs had shorter durations of untreated psychosis (9,21). This suggests that networking and education can lead to speedier detection. These specialized early identification programs may be more efficient than the genetic high-risk approach because between 30–50% developed psychotic disorders within a relatively short follow-up period (20,22–25). This superior efficiency in the Falloon-McGorry approach to early identification of psychotic disorders has led to radical changes in mental health services delivery in countries such as Australia, Norway, United Kingdom and Canada. In these countries, special programs have been set up to identify and treat psychotic patients early. Although these results are very encouraging, there is a need for replication in larger samples, as well as additional clarification regarding the positive predictive value for schizophrenia per se. Moreover, besides using prodromal and/or psychotic symptoms as the primary risk indicator, what other ways are there to detect schizophrenia early in its course (26,27)? Will the sensitivity, specificity, and predictive values of alternative approaches be at least comparable, if not better? How feasible is it to screen for schizophrenia prior to the overt manifestation of psychotic symptoms (28,29)?

In schizophrenia, psychotic symptoms are often preceded by subtle, non-specific behavioral and neuromotor cues that are observable as early as childhood (30–35). In their seminal descriptions of the disorder, both Kraepelin and Bleuler noted that some patients already stood out as children because of their social, personality and intellectual characteristics. Subsequent genetic high-risk studies (36), follow-back studies (e.g. 34,35,37,38), and birth-cohort and military conscript-cohort studies (39–43) provide empirical support for Bleuler's view that these 'character anomalies' may be the first expressions of schizophrenia. Thus, this wide range of precursors could be used in the early identification of schizophrenia (31,33,34,38,44–47).

The aim of this study is to examine the utility of one such precursor (i.e. premorbid cognitive impairment) in screening for schizophrenia. Standardized achievement tests provide a measure of premorbid cognitive functioning for a disease that is increasingly viewed as a disorder of cognition (48). Poor school performance has been well documented in children who went on to develop schizophrenia (39,40,42,43,49–54). Our group has previously reported that poor or declining scholastic performance may be a precursor to cognitive impairment in schizophrenia (55). To investigate the value of premorbid cognitive impairment in the early detection of schizophrenia, we 1) compared schizophrenia patients against a non-schizophrenia comparison group on a widely-used standardized achievement test (Iowa Tests of Basic Skills (ITBS) and Iowa Tests of Educational Development (ITED)), and 2) examined the sensitivity, specificity and positive predictive value of ITBS/ITED scores on the development of schizophrenia.

METHODS

Subject Selection and Assessment

Seventy patient subjects were recruited through the University of Iowa Mental Health Clinical Research Center. They were selected based on having DSM-IV schizophrenia, and having attended schools in Iowa. The latter criterion enabled the ITBS/ITED test scores to be traced from the University of Iowa College of Education, which maintains a database of test scores on Iowa students only. Patient subjects were evaluated using the Comprehensive Assessment of Symptoms and History (56), a structured interview instrument. The mean age of illness onset was 21.5 years (SD=4.63).

The 147 comparison subjects in this report have been participants in an adoption study (57), and have also attended schools in Iowa. They were interviewed as adults (mean age=26.0 years, SD=6.64) using the Diagnostic Interview Schedule (58) to assess lifetime prevalence of psychiatric illness. Thirty-six comparison subjects had no psychiatric disorders. Alcohol abuse/dependence (66.7%), drug abuse/dependence (34.7%), and major depressive disorder (29.9%) were most prevalent, and were frequently co-morbid. However, none of the comparison subjects had schizophrenic disorders, paranoid disorders, or psychotic disorders not elsewhere classified. This makes a valuable comparison group for testing the predictive value of premorbid cognitive impairment as a screening tool for schizophrenia versus other mental illnesses that typically have their onset in adolescence or young adult life.

There was a significantly greater proportion of male subjects in the schizophrenia group (81.4% versus 42.9% in the comparison group; χ^2=28.5, df=1, p<0.0001). Comparison subjects were of significantly higher parental socioeconomic status (SES) (Hollingshead-Redlich Two-Factor Index of Social Position (59) Mean=32.6 versus 53.2 in schizophrenia patients; T=8.91, df=214, p<0.0001). This is consistent with adoption practices where parents with higher SES are favored.

Standardized Achievement Tests

The ITBS and ITED have been used to measure scholastic achievement and critical thinking skills among Iowa school children for more than 30 years. These two standardized achievement tests assess seven basic curricular domains: Vocabulary, Reading, Language, Mathematics, Sources of Information, Social Studies, and Science (60,61). Together, the ITBS and ITED provide a continuous and vertically equated scale spanning from kindergarten through 12th grade. Details of individual sub-tests have been previously described (55). As Social Studies and Science sub-tests were optional components before 1992, the majority of our subjects did not receive these subtests. Therefore, only Vocabulary, Reading, Language, Mathematics, Sources of Information and Composite (or mean of the 5 sub-tests) Local Percentile Rank scores at Grade 4 (age 9–10 years), Grade 8 (age 13–14) and Grade 11 (age 16–17) were examined. The Local Percentile Rank shows a student's standing within all students in his/her grade in the State of Iowa.

Statistical Analysis

There were significant gender differences in percentile ranks (males scored lower: T's>2.34, df=159, p's<0.02). Higher parental SES correlated with lower ITBS/ITED scores (Spearman r's>0.20, df=158, p's<0.001). Hence, gender and parental SES were entered as covariates in between-group analyses. Receiver operating characteristic (ROC) curves were plotted to evaluate the efficiency of ITBS/ITED scores in differentiating schizophrenia subjects from comparison subjects (62,63). Sensitivity of a test is defined as the proportion of individuals with the disorder who are also classified positive on the test. Specificity is the proportion of individuals without the disorder classified negative on the test. Positive predictive value (or the probability of having the disorder given a positive test) of a test is highly dependent on its specificity, with high specificities correlating with high positive predictive values. Hence, we used specificity values of 80% and 90% to illustrate the utility of ITBS/ITED scores in screening for schizophrenia in the general population, and in a population of offspring of patients with schizophrenia. All tests of significance were two-sided.

RESULTS

The mean percentile ranks of schizophrenia subjects were consistently below the median (Figure 1). A pattern of decrement in Grade 11 scores among schizophrenia subjects was also observed. In addition, schizophrenia subjects had lower mean percentile ranks than comparison subjects in every sub-test at all three grades. The greatest differences were again in Grade 11

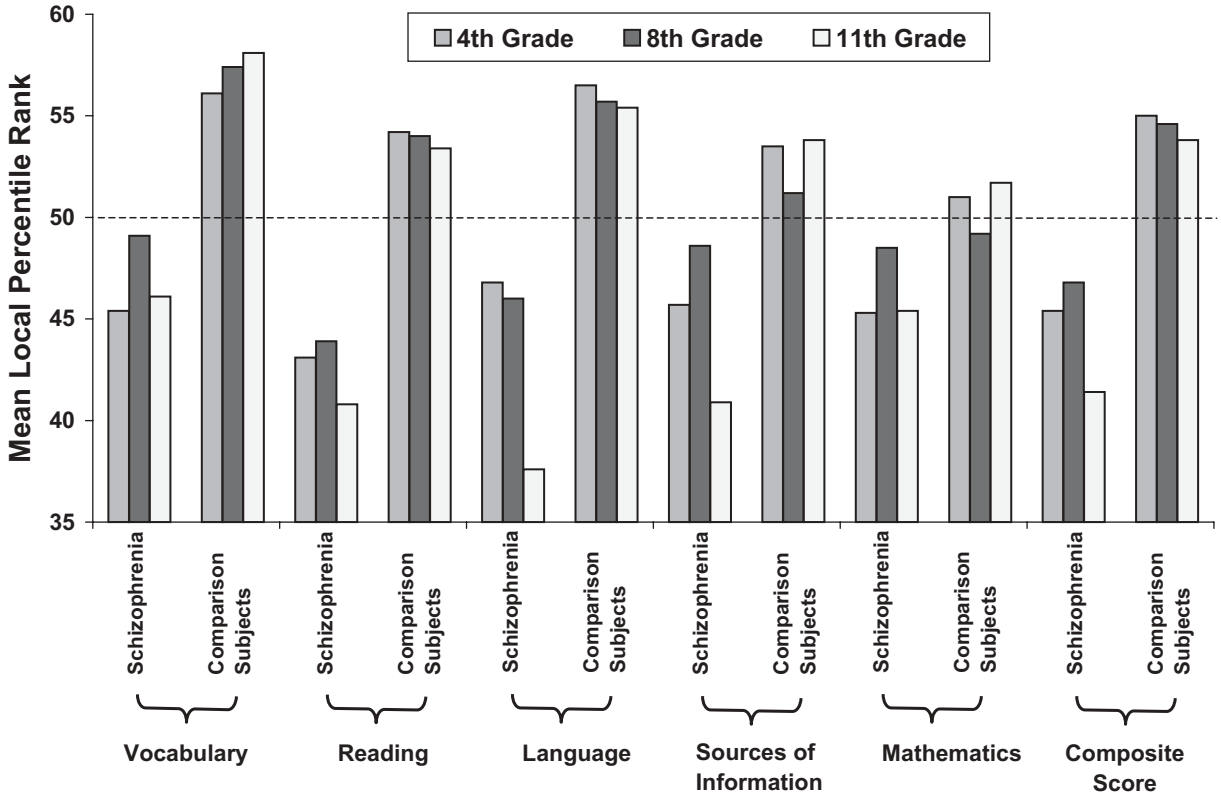

Figure 1 Mean Local Percentile Ranks for *Iowa Tests of Basic Skills* and *Iowa Tests of Educational Development* in 70 schizophrenia subjects and 147 comparison subjects.

(Table 1), where effect sizes were moderate to large (Cohen's d's ranging from 0.62 to 0.22). However, these effect sizes diminished substantially when gender and parental SES were co-varied (adjusted effect sizes < 0.17). Nevertheless, lower Grade 11 percentile ranks were associated with mildly increased risk for schizophrenia (odds ratios ranging 1.05 to 1.45).

We have previously reported that Language and Sources of Information scores differed significantly over time in schizophrenia subjects (55). To evaluate the efficiency of standardized achievement tests scores in differentiating schizophrenia subjects from comparison subjects, four ROC curves were plotted using test scores from the three grades: Language scores only, Sources of Information scores only, both Language and Sources of Information scores, and all test scores (Figure 2). Using all test scores best discriminated schizophrenia subjects from comparison subjects. The Sources of Information ROC curve did the poorest. Combining both Language and Sources of Information scores did not substantially improve on the discriminatory value of Language scores alone.

The corresponding sensitivity for specificities of 80% and 90% was obtained by reading from the Y-axis in Figure 2. Using each set of sensitivity and specificity values, the positive predictive values of the achievement tests were calculated for two scenarios: in the general population and in the population of offspring of patients with schizophrenia. The results are summarized in Table 2. Using all achievement test scores, a specificity of 80% yielded sensitivity of 75% while a more stringent specificity of 90% lowered the sensitivity to 47.5%. If this potential screening tool were to be applied to the general population (prevalence of schizophrenia=1%), its positive predictive value may be as high as 4.6%. Similarly, in a sample of offspring of patients with schizophrenia, adding ITBS/ITED performance data may enhance the detection of schizophrenia from 10% to as high as 34.5%.

To further assess the sensitivity and specificity of ITBS/ITED scores in delineating schizophrenia from substance use disorders and affective disorders, the comparison group was divided into healthy subjects (N=36), subjects with alcohol and/or substance use disorders only (N=64), and those with comorbid major depression and alcohol and/or substance use disorders (N=47). ROC curves were plotted using all test scores comparing schizophrenia subjects against each of these 3 sub-groups (Figure 3). Moderate levels of sensitivity and specificity were again obtained in these sub-group comparisons. In general, the highest levels of sensitivity and specificity were found in the schizophrenia-comorbid depression and substance use disorders comparison. These were followed by schizophrenia-healthy and then schizophrenia-substance use disorders only comparisons. Age of onset of alcohol use, age of onset of illicit substance use, severity of alcohol use, severity of illicit substance use, and parental SES were not significantly different between the two alcohol and/or substance use disorders comparison sub-groups (t's<1.48; df's=32 to 58; p's>0.15).

Table 1 Grade 11 Test Scores (percentile ranks) in Schizophrenia and Comparison Subjects

	Schizophrenia mean (SD)	Comparison subjects mean (SD)	Mean difference	Odds ratio[1] (95% CI)
Vocabulary	46.1 (30.1)	58.1 (28.9)	12.0	1.18 (1.03-1.36)
Reading	40.8 (30.1)	53.4 (32.3)	12.7	1.17 (1.02-1.35)
Language	37.6 (29.8)	55.4 (28.4)	17.8	1.45 (1.07-1.80)
Sources of Information	40.9 (31.7)	53.8 (29.3)	12.9	1.20 (1.04-1.39)
Mathematics	45.4 (29.4)	51.7 (27.7)	6.3	1.05 (0.98-1.13)
Composite score	41.4 (29.9)	53.8 (29.5)	12.4	1.19 (1.03-1.37)

[1]Based on observed mean difference

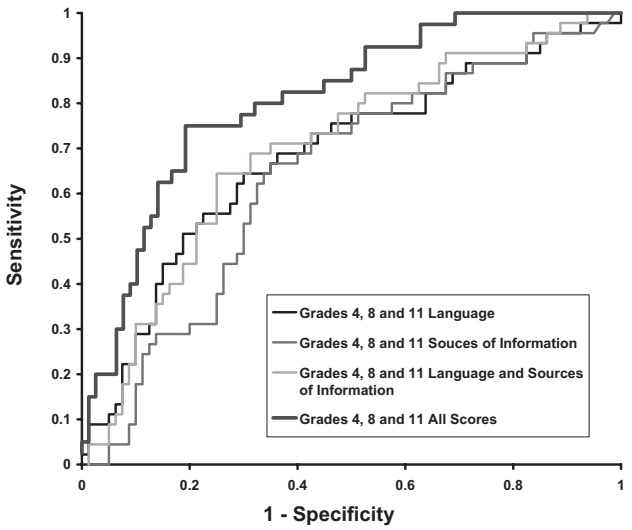

Figure 2 Receiver operating characteristic curves for four potential screening tools.

Table 2 The Sensitivity and Positive Predictive Value of Potential Screening Tools Using Standardized Achievement Test Scores

	Specificity = 80 %			Specificity = 90 %		
Potential screening tools	Percent Sensitivity	PPV[1]	PPV[2]	Percent Sensitivity	PPV[1]	PPV[2]
Language scores only	51.1	2.5	22.1	28.9	2.8	24.3
Sources of Information scores only	31.1	1.5	14.7	17.8	1.8	16.5
Language and Sources of Information scores	44.4	2.2	19.8	31.1	3.0	25.7
All scores	75.0	3.6	29.4	47.5	4.6	34.5

[1]PPV = Positive Predictive Value (Percent), based on 1% prevalence of schizophrenia in the general population.
[2]PPV = Positive Predictive Value (Percent), based on 10% prevalence of schizophrenia among offspring of patients with schizophrenia.

DISCUSSION

In this study, we examined the feasibility of employing a widely-used scholastic test in the United States for early detection

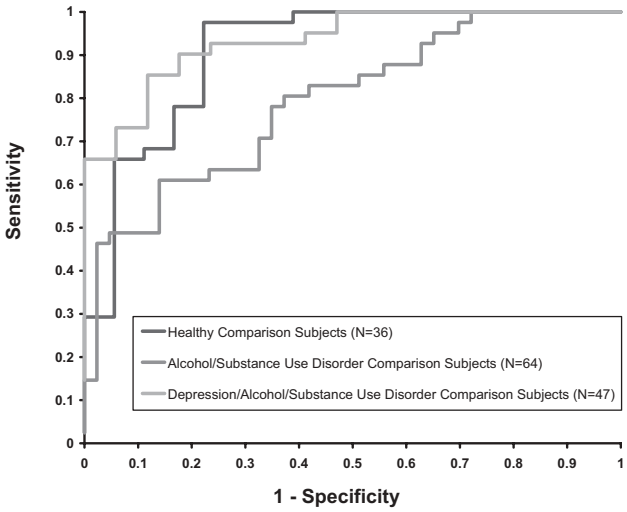

Figure 3 Receiver operating characteristic curves: Comparative sensitivity and specificity of *Iowa Tests of Basic Skills* and *Iowa Tests of Educational Development* test scores in differentiating between patients with schizophrenia from healthy comparison subjects, subjects with alcohol and/or substance use disorders, and subjects with co-morbid depression and alcohol and/or substance use disorders.

of schizophrenia. Although patients with schizophrenia had lower mean percentile ranks in every sub-test examined, the largest between-group differences (seen in Grade 11) were only associated with small increases in risk for schizophrenia. Even though standardized achievement tests were moderately sensitive and specific, and enhanced the detection of schizophrenia in the general population by almost five fold, their efficiency in screening for schizophrenia was poor because positive predictive values were low. Our findings illustrate the difficulties in predicting schizophrenia in the general population. Combining achievement test scores with other risk factors, such as family history, may lead to more efficient early detection of schizophrenia. Unlike the low specificity of prodromal symptoms (64,65), standardized achievement test scores appear to be moderately specific in differentiating schizophrenia from substance use disorders and affective disorders, which typically also have their onset in adolescence or young adult life as well.

Secondary prevention is aimed at early detection, prompt treatment, and cure for a disease at its earliest stages. When cure is unattainable, the goals are to reduce disease progression and prevent complications and disability. This strategy has been successful in reducing morbidity and mortality of breast and colorectal cancers. In schizophrenia, the potential benefits of early intervention have been well recognized (9,33,46,66,67). Schizophrenia, the most severe of mental disorders, is a devastating illness that often leads to lifelong disability. It places enormous burdens on the society. Despite advances in treatment, none of the proven treatments actually cures the illness. Neuroleptic medications, family psychoeducation, and assertive community outreach only reduce relapses, decrease family burden, and maintain the individual in the community. Current therapeutic limitations, together with the protracted treatment delays (1–12), compel the field to examine the role of prevention.

However, before the potential of secondary prevention can be realized, several methodological and ethical issues will need to be resolved. One challenge confronting schizophrenia prevention today is finding the most efficacious early interventions, since available medications are 'antipsychotic' and may be less effective during the early pre-psychotic phase of the illness. However, the biggest hurdle may be the lack of good screening tools for accurate early identification. This is compounded by the relatively low prevalence of schizophrenia in the general population. Previous studies (68–70) as well as our findings indicate that low disease base rates magnify the prediction errors of screening programs. Although ITBS/ITED scores achieved moderate sensitivity and specificity, and enhanced the selection of at-risk subjects by three to five fold, greater than 95% of individuals screened positive may never develop schizophrenia. Besides schizophrenia, poor scholastic performance may also arise from other causes. Reasons for poor ITBS/ITED test scores are diverse, and include other psychiatric disorders (e.g., depressive illness, conduct disorder, substance misuse), inheritable factors that determine general intellectual abilities, as well as environmental factors. Therefore, ITBS/ITED scores alone will not be an efficient screening method for early detection of schizophrenia.

Similar problems have plagued early intervention programs to-date. Early efforts to prevent schizophrenia focused on offspring of patients with schizophrenia (36). While this genetic high-risk approach has had limited efficiency in early detection (36,71), recent early intervention programs appear to be more promising. Using prodromal and/or psychotic symptoms as the primary risk indicator, 30–50% of patients in these programs have developed psychotic disorders within a relatively short period. However, the predictive values for schizophrenia will not be known until these individuals have been followed beyond the age of risk. In the meantime, there is a need for testing alternative approaches and developing efficient screening methods. Several solutions have been proposed to help circumvent problems stemming from low disease base rate, and from low specificity of risk indicators for schizophrenia (72–76).

Since each individual risk factor (e.g., family history, prodromal symptoms, standardized scholastic tests) has limited power to predict the development of schizophrenia, a promising strategy in secondary prevention may be to combine a group of different risk factors into a multi-stage screening program. Such combinations can result in improved predictive power and lower false positive rates. Loeber and colleagues demonstrated that a three-stage 'multiple-gating procedure' was not only less expensive, but each successive 'gate' also improved the positive predictive value in screening for delinquent youths (72). In schizophrenia, a wide range of precursors and risk factors may serve as potential 'gates'. For example, ITBS/ITED could be the first gate since achievement tests are already commonly administered in schools. Declining ITBS/ITED scores lead to the second gate where teachers rate students on social

withdrawal, aggression and anxiety. Students screened positive then undergo a third gate to assess for cognitive deficits associated with schizophrenia (e.g., impaired attention, working memory, and executive functioning). Through such a multistage screening process, an enriched sample where a reasonably high proportion will develop schizophrenia may be derived for further studies in prevention.

Prevention of schizophrenia may become more feasible if schizophrenia were one of several disorders targeted for prevention in a broad-base preventive program. The behavioral and intellectual precursors to schizophrenia are not specific to the disorder, and have been associated with affective disorders (77), other psychotic disorders (50), and personality disorders and substance use disorders (51). A proportion of the false positives for schizophrenia would be true positives for other psychiatric disorders. Hence, the high-risk sample becomes a 'multiple-risk cohort' (73), and the low specificity of these precursors for individual disorders can be turned into an advantage—'prevent one and you prevent them all' (75,76).

CONCLUSIONS

Screening constitutes the cornerstone of secondary prevention. Through screening, cases are brought to early treatment so as to improve outcome and survival. Efficient screening not only reduces the dangers of making erroneous false positive diagnoses, it also decreases exposure to unnecessary treatment during the testing of early interventions. In schizophrenia, we need to focus on developing more efficient methods of early detection first. We may not be ready for early intervention yet because current early detection methods have unacceptably high false positive rates. Furthermore, it is unclear which aspects of schizophrenia require prophylactic intervention. But, will early intervention ultimately lead to improved outcome? That's what we need to find out.

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