Published in final edited form as:
Arch Gen Psychiatry. 2008 January ; 65(1): 28–37. doi:10.1001/archgenpsychiatry.2007.3.

Prediction of Psychosis in Youth at High Clinical Risk:

A Multisite Longitudinal Study in North America

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Abstract

Context—Early detection and prospective evaluation of individuals who will develop schizophrenia or other psychotic disorders are critical to efforts to isolate mechanisms underlying psychosis onset and to the testing of preventive interventions, but existing risk prediction approaches have achieved only modest predictive accuracy.

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Author Contributions: Drs Cannon and Cadenhead had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Financial Disclosures: Dr Cannon reports receiving investigator-initiated research funding support from multiple not-for-profit entities, including the National Institute for Mental Health (NIMH), the National Alliance for Research on Schizophrenia and Depression (NARSAD), and the Staglin Music Festival for Mental Health; and has served as a consultant to Janssen Pharmaceuticals and Eli Lilly and Co. Dr Cadenhead reports receiving investigator-initiated research funding support from the NIMH. Dr Cornblatt reports receiving investigator-initiated research funding support from not-for-profit entities, including the NIMH and the Stanley Medical Research Institute; has served as a consultant to Eli Lilly and Co, Bristol-Meyers Squibb, and Janssen Pharmaceuticals; and reports receiving unrestricted educational grants from Janssen Pharmaceuticals. Dr Woods reports receiving investigator-initiated research funding support from multiple not-for-profit entities, including the NIMH and the Donaghue, Stanley, and NARSAD foundation; and reports receiving investigator-initiated research funding support from multiple for-profit entities, including Eli Lilly and Co, Janssen Pharmaceuticals, UCB Pharma, and Bristol-Myers Squibb. Dr Addington reports receiving investigator-initiated research funding support from multiple not-for-profit entities, including the NIMH and Ontario Mental Health Foundation; and has served as a consultant to Pfizer Inc, Astra-Zenca, and Janssen Pharmaceuticals. Dr Walker reports receiving investigator-initiated research funding support from not-for-profit entities, including the NIMH and NARSAD. Dr Seidman reports receiving investigator-initiated research funding support from multiple not-for-profit entities, including the NIMH, the March of Dimes Foundation, the Mental Illness Neuroscience Discovery Institute, the Commonwealth of Massachusetts Department of Mental Health, and the National Association for Research in Schizophrenia and Depression; has served as a consultant to Shire, Eli Lilly and Co, and Janssen Pharmaceuticals; and reports receiving an unrestricted educational grant from Janssen Pharmaceuticals. Dr Perkins reports receiving research funding from AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb, Otsuka Pharmaceutical Co Ltd, Eli Lilly and Co, Janssen Pharmaceutica Products, and Pfizer Inc, and consulting and educational fees from AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb, Eli Lilly and Co, Janssen Pharmaceuticals, GlaxoSmithKline, Forest Labs, Pfizer Inc, and Shire. Dr McGlashan reports receiving investigator-initiated research funding support from the NIMH, the Personality Disorder Research Foundation, and Eli Lilly and Co; and has served as a consultant to Eli Lilly and Co, Pfizer Inc, Solvay/Wyeth, and Roche Pharmaceuticals.

Objectives—To determine the risk of conversion to psychosis and to evaluate a set of prediction algorithms maximizing positive predictive power in a clinical high-risk sample.

Design, Setting, and Participants—Longitudinal study with a 2½-year follow-up of 291 prospectively identified treatment-seeking patients meeting Structured Interview for Prodromal Syndromes criteria. The patients were recruited and underwent evaluation across 8 clinical research centers as part of the North American Prodrome Longitudinal Study.

Main Outcome Measure—Time to conversion to a fully psychotic form of mental illness.

Results—The risk of conversion to psychosis was 35%, with a decelerating rate of transition during the 2½-year follow-up. Five features assessed at baseline contributed uniquely to the prediction of psychosis: a genetic risk for schizophrenia with recent deterioration in functioning, higher levels of unusual thought content, higher levels of suspicion/paranoia, greater social impairment, and a history of substance abuse. Prediction algorithms combining 2 or 3 of these variables resulted in dramatic increases in positive predictive power (ie, 68%–80%) compared with the prodromal criteria alone.

Conclusions—These findings demonstrate that prospective ascertainment of individuals at risk for psychosis is feasible, with a level of predictive accuracy comparable to that in other areas of preventive medicine. They provide a benchmark for the rate and shape of the psychosis risk function against which standardized preventive intervention programs can be compared.

Can prevention models now common to medicine be applied to psychotic disorders? Advances in early detection and intervention in cardiovascular disease,[1] diabetes mellitus,[2] and cancer[3,4] have led to substantial reductions in morbidity and mortality and improved quality of life among individuals with these conditions. Efforts to extend such a prevention approach to schizophrenia have focused on developing and validating criteria for ascertaining individuals at risk for imminent onset of psychosis (ie, clinical high-risk or prodromal patients) and following them over time.[5–7] The aims are to improve understanding of the mechanisms of disease onset and progression and to facilitate application of interventions before the illness takes hold, thereby reducing or preventing the devastating effects of schizophrenia. An advantage of this approach over high-risk methods based on a family history of schizophrenia is that assessments can be timed much more efficiently in relation to the onset of disorder.[8]

Using empirically defined criteria for a high-risk clinical state that emphasize recent onset or worsening of subsyndromal psychotic symptoms,[9,10] previous studies have reported conversion rates of 9% to 76% in sample sizes of 13 to 110 subjects across 1- to 9-year follow-up intervals.[11–19] Much larger numbers of cases are required to provide statistically reliable modeling of the survival curve and estimates of the positive predictive power (PPP) of existing prodromal criteria. In addition, there is a great deal of variability in the assessment methods, sample characteristics, and length and frequency of follow-up across these studies.[11]

The North American Prodrome Longitudinal Study[20] is a consortium of 8 research centers, each organized around the goal of improving the accuracy of prospective prediction of initial psychosis by ascertaining individuals who are at high clinical risk and following them at regular intervals for up to 2½ years. Although the research centers originally developed independent studies, they used similar ascertainment and longitudinal assessment methods, making it possible to form a standardized protocol for mapping acquired data into a new scheme representing the common components across the sites.[20] This method yielded the largest database of prodromal cases followed up longitudinally worldwide (291 cases).

The primary aims of this study were to determine the rate of conversion to psychosis, to ascertain the shape of the survival function across 2½ years of follow-up, and to develop a multivariate risk prediction algorithm to guide the selection of cases in future studies. Included in the list of potential predictors were variables found to be associated with risk of conversion to psychosis in previous studies of smaller samples, including genetic risk for schizophrenia,[8,21,22] severity of prodromal symptoms,[11] severity of nonspecific symptoms,[19] social and role functioning,[19,23,24] and substance abuse.[25–29] It was hypothesized that a subset of these variables would contribute uniquely to the prediction of psychosis and combine into a multivariate algorithm with higher PPP compared with prodromal syndrome criteria alone.

METHODS

SAMPLE ASCERTAINMENT AND ASSESSMENT

The study protocols and informed consent documents, including procedures for data pooling, were reviewed and approved by the institutional review boards of the 8 participating study sites (Emory University; Harvard Medical School; University of California, Los Angeles; University of California, San Diego; University of North Carolina, Chapel Hill; University of Toronto; Yale University; and Zucker Hillside Hospital). Each site recruited potential subjects through clinical referrals as stimulated by talks to school counselors and mental health professionals in community settings. At each site, from 30% to 50% of the referred case patients met Structured Interview for Prodromal Syndromes (SIPS)[9,13] criteria for study entry. Training workshops, conducted by Miller et al[9,13] for the interviewers at each site, included lectures, group rating exercises, and detailed discussion of operational criteria used for diagnostic classification. Post-training agreement with the Yale University expert raters on the distinction between prodromal and psychotic levels of intensity on the positive symptom items (ie, the critical threshold for determining initial eligibility and subsequent conversion status) was excellent overall (κ, 0.90) and at each of the sites (κ range, 0.80–1.00).[20] At each site, the raters were mental health specialists with academic credentials consisting of doctorates of medicine, master's degrees, or doctorates of philosophy. New raters added during the course of the study had to achieve agreement standards with the training set before conducting assessments.

The SIPS criteria[9] for a prodromal syndrome emphasize onset or worsening in the past 12 months of attenuated positive symptoms in 1 or more of 5 possible categories: unusual thought content, suspicion/paranoia, perceptual anomalies, grandiosity, and disorganized communication. A 7-point severity scale is used for each symptom, reflecting its frequency, duration, impact on functioning, and degree of loss of insight. Levels of 0 to 2 (none, questionable, or mild) indicate normal to sub-prodromal functioning; levels of 3 to 5 (moderate, moderately severe, or severe), a prodromal state; and a level of 6, a fully psychotic state. For example, a prodromal level of unusual thought content corresponds to an idea of reference or an odd belief that is worrisome or becomes meaningful because it will not go away and may be accompanied by an emerging sense that the event is caused by an external source, but doubt in this notion can be induced by contrary evidence. By contrast, a psychotic level of unusual thought content is an idea of reference or odd belief that is accompanied by full conviction for a specified period or that is acutely disruptive or disabling. The instrument is used to rate the severity of symptoms and to derive a categorical determination of prodromal status.

A subject may also qualify for a prodromal syndrome on the SIPS because of onset in the past 3 months of brief intermittent psychotic symptoms, which are positive symptoms of psychotic intensity but below the threshold required for a *DSM-IV* Axis I psychotic disorder diagnosis, or by having a genetic risk (defined as having a first-degree relative with a

psychotic disorder or as having a diagnosis of schizotypal personality disorder) for psychosis and deterioration of 30% or greater on the General Assessment of Functioning Scale in the past 12 months. A genetic relationship between schizophrenia and schizotypal personality disorder has been detected in samples of families, twins, and adoptees.[30–36]

BASELINE ASSESSMENT PROTOCOL

All sites collected information on demographics, prodromal symptom severity,[13] family history of mental illness,[37] schizotypal personality disorder diagnosis,[9] social and role functioning,[38] comorbid psychiatric diagnoses (as assessed by the Structured Clinical Interview for *DSM-IV*[39] or the Schedule for Affective Disorders and Schizophrenia for School-Age Children),[40] and substance abuse (as assessed by the Structured Clinical Interview for *DSM-IV* or the Schedule for Affective Disorders and Schizophrenia for School-Age Children). For all of these variables except social and role functioning, the same instruments were used across sites, permitting straightforward data integration. For the functioning measures, the original data were recoded at each site using new scales developed specifically for this study and shown to have favorable psychometric properties in a reliability/ validity study.[38] Further details of the construction of the federated database are published elsewhere.[20]

FOLLOW-UP ASSESSMENTS

The SIPS was readministered at 6-month intervals to a maximum of 30 months. If case managers observed clinical deterioration in the patients under their care, a reassessment was conducted between regularly scheduled assessments. The primary outcome variable for this study was time from baseline evaluation to conversion to psychosis according to SIPS criteria. A SIPS diagnosis of a psychotic syndrome refers to psychotic symptoms of particular intensity (eg, delusional conviction) and frequency or duration (≥1 h/d for ≥4 d/ wk during the past month) or of particular impact (seriously disorganizing or dangerous), designed to operationalize the threshold for a *DSM-IV*[41] Axis I psychotic disorder diagnosis. Psychosis is the primary defining feature of schizophrenia but may occur in a number of other *DSM-IV* categories, including bipolar disorder and major depression. The Structured Clinical Interview for *DSM-IV* was not applied across all of the sites at follow-up to enable examination of the particular *DSM-IV* diagnoses attained at the point of conversion.

ANTIPSYCHOTIC TREATMENT

Of the 370 patients in the study, 83 (22.4%) were enrolled as participants in a randomized comparison of olanzapine vs placebo[42] or in other small prospective treatment studies, and the remaining 287 (77.6%) were enrolled as participants in a longitudinal follow-up study with treatment of diagnosable symptoms provided on- or off-site when indicated in the view of the treating physician according to his or her interpretation of the standards for usual and customary care. Because treatment was not standardized across patients or sites, information on the dosing and duration of antipsychotic treatments was not available for most of the cases, but sites were able to indicate whether each case patient received antipsychotic drug treatment during the follow-up.

STATISTICAL ANALYSES

We used Kaplan-Meier survival analysis to ascertain the shape of the survival function during the 2½-year follow-up interval, the cumulative rate of conversion, and the incidence rates of conversion within successive 6-month epochs. We also sought to derive a multivariate algorithm that optimizes prediction of conversion to psychosis using the Cox proportional hazards model. In this form of analysis, predictors are modeled in relation to the time since baseline to conversion to psychosis, and subjects who do not experience

conversion contribute to the prediction until they are no longer available for observation, at which point they are considered censored. A large number of potential predictor variables were available from the baseline assessment, and many of them would be expected to overlap with each other in relation to outcome. Separate multivariate Cox regressions were used to screen sets of potential predictor variables within the following 10 domains: sociodemographic characteristics, genetic risk for schizophrenia, positive and negative symptoms, disorganization, general symptoms, comorbid psychiatric diagnoses, social and role functioning, substance abuse, and antipsychotic drug treatment during the follow-up interval. These analyses used a backward selection approach to ascertain variables that have unique predictive associations with conversion at an initially liberal threshold of $P<.10$. We then performed an omnibus regression in which variables found to contribute uniquely to conversion in the initial series were considered together. Variables that remained significant at $P<.05$ in the omnibus analysis were then evaluated for multiplicative (interaction) effects in relation to conversion using the Lifetest procedure in SAS statistical software.[43] In addition to the hazards ratio, we monitored the PPP and the sensitivity of each predictor or each combination of predictors.

RESULTS

SAMPLE CHARACTERISTICS AND TESTS OF ATTRITION BIAS

Of the 370 subjects enrolled in the study, 291 (78.6%) completed at least 1 subsequent clinical evaluation, and 79 (21.4%) were lost to follow-up. As shown in Table 1, the patients with follow-up information did not differ significantly from those lost to follow-up in terms of age; parental education; severity of positive or negative symptoms; social, role, and global functioning; SIPS subdiagnosis; race; ethnicity; year of study entry; schizotypal personality disorder diagnosis; presence of a first-degree relative with psychosis; or presence of a first- or second-degree relative with psychosis. Sex was the only significant effect related to attrition, with a higher percentage of male patients among those lost to follow-up compared with the percentage of male patients among those successfully followed up (ie, 74.7% vs 58.4%).

KAPLAN-MEIER SURVIVAL CURVE

Eighty-two of the 291 patients experienced conversion to psychosis (hereinafter referred to as converted cases), with a mean±SD time to conversion of 275.5±243.7 days since the baseline evaluation. Seventy-nine of the 82 converted cases met initial eligibility based on attenuated positive symptoms and 3 met initial eligibility based on brief intermittent psychotic symptoms (the corresponding numbers for the nonconverted cases were 203 and 6, respectively). Although only 2 patients were ascertained as prodromal exclusively in the genetic risk and deterioration category, 16 of the converted cases (and 18 of the nonconverted case) had a comorbid attenuated positive symptoms–genetic risk and deterioration prodromal diagnosis. The 209 nonconverted cases were followed up for a mean ±SD of 575.4±258.4 days since the baseline assessment. Antipsychotic medications were prescribed for 35.1% of the patients during the follow-up interval. The Figure plots the Kaplan-Meier survival curve reflecting the percentage of subjects who did not experience conversion to psychosis (here in after referred to as nonconverted cases) during the 2½-year follow-up. The cumulative prevalence rate±SE of conversion to psychosis was 12.7%±1.9% at 6 months, 21.7%±2.5% at 12 months, 26.8%±2.8% at 18 months, 32.6%±3.3% at 24 months, and 35.3%±3.7% at 30 months. Thus, the SIPS criteria alone are associated with a PPP of 35% during 2½ years of follow-up. The incidence rate of conversion shows an overall decelerating trend during the follow-up period; this rate is 13% in the first 6 months, slows modestly to 9% from 7 to 12 months, slows to 5% per each 6-month epoch at 13 to 24 months, and then slows again to 2.7% from 25 to 30 months. For comparison, there were no

conversions during this period among 134 normal control subjects who were matched demographically (by age, sex, and ethnicity) with the prodromal patients.

SCREENING OF POTENTIAL PREDICTORS

Of the 77 potential predictor variables examined (Table 2), 37 were associated with conversion to psychosis in univariate analyses. As shown in Table 3, when multivariate analysis was applied to sets of predictors from each assessment domain, which effectively removes redundancy among related measures, the number of predictors meeting the cutoff for inclusion fell to 16. Treatment with antipsychotic drugs during the follow-up interval was associated with a significant increase in risk of conversion (hazard ratio, 1.55).

When the 16 predictors that survived domain-wise multivariate screening were examined in an omnibus (cross-domain) multivariate analysis, conversion to psychosis continued to be related significantly and uniquely to genetic risk for schizophrenia with recent functional deterioration (χ^2=10.45; *P*=.001), unusual thought content (χ^2=6.36; *P*=.01), suspicion/paranoia (χ^2=9.24; *P*=.002), social impairment (χ^2=14.98; *P*<.001), and history of any drug abuse (χ^2=6.82; *P*=.009). With these terms in the model, none of the other predictors that had survived the domain-wise screening procedure (Table 3) were related to conversion risk, indicating that their predictive associations were redundant with the other model terms. In particular, treatment with antipsychotic drugs during the follow-up interval was not significantly associated with conversion in the cross-domain multivariate analysis (χ^2=0.59; *P*=.44).

MULTIVARIATE PREDICTION ALGORITHMS

Prediction statistics for each of the 5 uniquely predictive variables and their 26 possible combinations are given in Table 4. These represent all of the combinatorial algorithms tested. At the univariate level, these factors have approximately equivalent PPP (ie, 43%–52%), and each is superior in this regard to the SIPS criteria alone (35%). Nevertheless, the adjunctive use of these predictors in determining risk status results in a reduction in sensitivity. Sensitivity is excellent for suspicion/paranoia and impaired social functioning (79% and 80%, respectively), moderate for genetic risk for schizophrenia with recent functional decline and unusual thought content (66% and 56%, respectively), and poor for history of substance abuse (29%). Among the algorithms requiring co-occurrence of 2 risk factors, the models including genetic risk for schizophrenia with recent functional decline and unusual thought content or impaired social functioning have the highest PPP (69% and 61%, respectively), both substantially higher than that of the 1-factor models, although sensitivity is again relatively modest (ie, 38% and 55%, respectively). Two of the 3-factor models, involving genetic risk for schizophrenia with recent functional decline, unusual thought content, and either suspicion/paranoia or impaired social functioning, result in even higher PPP (74% and 81%, respectively) compared with the 2-factor models, with only marginal additional loss in sensitivity, and there is no further gain in prediction among any of the 4-factor models or the 5-factor model. Multivariate algorithms not requiring co-occurrence of risk factors have lower PPP (ie, 40%–45%) but substantially higher sensitivity (ie, 70%–95%) compared with those in Table 4. In addition, the algorithm reflecting the sum of the 5 independent risk factors is no better in terms of PPP (ie, 77%–79% among those with 4 or 5 factors) than the best-performing 3–coincident factor model.

Controlling for antipsychotic drugs during the follow-up interval did not modify the significance or the magnitude of the results for the 5 uniquely predictive variables and their 26 possible combinations shown in Table 4.

COMMENT

The operationally defined criteria for prodromal schizophrenia show substantial predictive validity. Thirty-five percent of individuals identified on the basis of recent onset or worsening of subsyndromal psychotic symptoms experienced conversion to psychosis after 2½ years of follow-up. To our knowledge, the current sample size of 291 is nearly 3 times larger than that of any previous study, providing greater statistical confidence in the survival estimates. This 2½-year conversion rate of 35.3% represents a relative risk of 405 compared with the incident rate of all forms of psychosis in the general population during a comparable period (ie, 0.087%, or 0.034% per annum).[45]

The survival curve has a decelerating trend, such that progressively fewer cases convert to psychosis with increasing length of follow-up. This finding indicates that the prodromal criteria are sensitive to risk for imminent onset and provide an empirical basis on which to time the application of preventive interventions. After 2½ years, the risk of onset of psychosis is 2.7%, still higher than the annual incidence rate of schizophrenia in the general population but significantly below the rate observed in the first year of follow-up (ie, 20%).

In the 2 largest previous studies of prodromal psychosis,[15,16] a conversion rate of 35% was observed among 104 clinical high-risk subjects identified using criteria comparable to the SIPS,[16] and a conversion rate of 49% was observed (after 9.6 years of follow-up) among 110 cases identified using the Bonn Scale of Basic Symptoms.[15] The Bonn Scale of Basic Symptoms emphasizes changes in social, emotional, and motivational factors and is thought to ascertain individuals in a much earlier stage of developing psychotic illness.[46]

Prediction algorithms incorporating combinations of 3 baseline variables (genetic risk for schizophrenia with recent functional decline, higher levels of unusual beliefs or suspiciousness, and greater social impairment) resulted in dramatic increases in PPP (74%–81%) compared with SIPS criteria alone (35%). These prediction algorithms were derived empirically, rather than confirmed through hypothesis testing. A relatively conservative empirical approach was used, such that we first screened the potential predictor variables for association with conversion in multivariate models within each assessment domain and retained only those variables that contributed uniquely to prediction in an overall (cross-domain) multivariate model for consideration in combinatorial algorithms maximizing PPP. Nevertheless, because the algorithms were derived empirically, they should be confirmed in an independent study with comparable sample size and selection, assessment, and follow-up criteria, as might be possible in future collaborations of the North American Prodrome Longitudinal Study group, as well as in similar collaborative efforts in Europe.[47]

Genetic risk for schizophrenia with recent functional deterioration was strongly and uniquely predictive of conversion to psychosis in this sample. Although the SIPS criteria include a prodromal syndrome involving genetic risk with a decline of 30% or more on the General Assessment of Functioning Scale in the past 12 months, patients who meet these criteria exclusively, without evidence of attenuated psychoticlike symptoms, are quite rare. Nevertheless, the risk construct implied by this category appears promising given that schizophrenia spectrum disorders are specifically elevated among first-degree relatives of patients with schizophrenia.[34,48,49] Thus, functional decline, although otherwise nonspecific, should be highly predictive of psychosis in those with a genetic background for the disorder. To model this possibility, we created a new genetic risk and functional deterioration metric in which the genetic component is defined as in the SIPS, but the functional deterioration requirement was relaxed to a criterion of decline of 10% or greater in social, role, or psychological functioning in the year before ascertainment, using scales developed specifically for use in adolescent and preonset samples.[38] This metric proved to

be a more sensitive predictor of conversion to psychosis than a family history of psychosis or schizotypal personality disorder, whose contributions to psychosis risk were not significant once the genetic risk with functional deterioration term was modeled.

Social deficits and prodromal symptom severity at baseline are also key predictors of psychosis. The present findings indicate that the poorer the social functioning and the more severe the subsyndromal symptoms at ascertainment, particularly in the domains of unusual thought content and suspiciousness, the closer the subject is to the onset of psychosis. Deficits in social functioning are among the most robust behavioral correlates of genetic risk for schizophrenia and are present in many at-risk individuals from childhood.[17,50–53] Given that social deficits and prodromal symptom severity combine with a genetic risk for schizophrenia and recent functional decline in achieving maximal prediction, the onset of psychosis appears to be marked by a changing course of thinking and functioning against a backdrop of preexisting inherited vulnerability traits.[17,22] In a previous study of 104 clinical high-risk patients from the Personal Assessment and Crisis Evaluation Clinic in Melbourne, Australia, the coincident requirement of meeting attenuated positive symptoms and genetic risk and deterioration criteria was associated with a PPP of 69% and a sensitivity of 31%.[19] The increased sample size in the present study enabled the evaluation of specific symptom predictors and varying thresholds for functional deterioration. The predictive validity of other positive symptoms, such as perceptual abnormalities and grandiosity, is limited by their relatively low base rates in this sample.

A history of substance abuse also predicted conversion, although in multivariate analyses no specific substance class of the 7 tested (ie, alcohol, hypnotics, cannabis, amphetamines, opiates, cocaine, and hallucinogens) was significantly associated with risk. It is possible that larger studies will be needed to determine whether specific substances are associated with psychosis in prodromal cases. Although the low base rate of substance abuse severely limits sensitivity, its association with conversion risk is theoretically important because a drug-related mechanism may be capable of producing psychosis-promoting changes in brain function in some high-risk patients. Furthermore, this association, if confirmed, suggests that abstinence from drugs may help to lower the risk of psychotic illness in this population.

Although rates of conversion were higher among cases ascertained in earlier years of the study than more recently, after controlling for other predictors, this effect was not significant. Given that most prodromal research programs have increasingly engaged in community outreach and education efforts to increase awareness of early warning signs, decrease stigma, and stimulate referral, a higher proportion of more recently recruited patients may be ascertained in an earlier phase of risk, when symptoms are less severe.[54] A decreasing transition rate could also reflect the increasing and/or more effective application of pharmacologic and psychosocial interventions in prodromal clinics and the community. Three preliminary studies support the notion that early intervention with either or both approaches is associated with prodromal symptom reduction and possibly with reduced or delayed risk for onset of psychosis.[42,55,56] Although most investigators in the prodromal field advocate a highly conservative approach to drug treatment of clinical high-risk individuals, whereby antipsychotic drug therapy is initiated only after symptoms have reached a fully psychotic level of intensity, community-based physicians may sometimes be less conservative. In addition, it is not unusual for clinical high-risk patients to receive psychosocial interventions in the community or in the prodromal research programs themselves because these interventions are generally indicated to address presenting complaints (eg, low motivation, social withdrawal, and school failure) and have a lower risk of adverse events than drug treatment.

In this study, antipsychotic drug treatment was found to be associated with a significant increase in risk of conversion to psychosis at the univariate level, most likely reflecting the fact that most of the patients were treated in naturalistic circumstances in which physicians prescribe antipsychotics in the presence of greater severity of positive symptoms. This effect disappeared in the cross-domain multivariate analyses controlling for symptom severity, and accounting for this treatment variable did not modify the predictive relationships between the other study variables and conversion risk. Thus, the predictive relationships between other risk indicators and conversion, the decelerating survival function, and the 35% conversion rate observed in this study appear to be statistically independent of the application of such treatments. A more rigorous basis for dissociating the effects of treatment from natural factors influencing the risk of conversion to psychosis may be possible in a formalized treatment study with random assignment of patients to an active treatment vs placebo. However, patients who consent to participation in randomized, placebo-controlled studies of antipsychotic drugs may differ in substantial ways from those who are willing to be followed up longitudinally while retaining choice over interventions received. More restrictive exclusion criteria (eg, owing to diagnostic comorbidities or the need for conjoint treatments) and attrition owing to the adverse effects of drug treatments further limit generalizability of prediction findings from samples drawn from randomized treatment studies.

In general, the multivariate algorithms, while achieving a considerably higher PPP than any of the univariate models, were associated with much lower sensitivity. This pattern reflects the lower base rates of coincident occurrences of risk factors. Allowing for noncoincident combinations of risk factors resolves this problem, yielding excellent sensitivity but at the sacrifice of PPP, which falls to the level of the univariate models. Sensitivity may be increased in multivariate algorithms integrating quantitative measures that may have more favorable distributional properties than clinical ratings, such as indicators of brain anatomy or physiology or neurocognitive performance.[57–62]

Attrition was unrelated to the primary variables that predicted conversion to psychosis in this sample. Although more male than female patients were lost to follow-up, conversion to psychosis did not vary according to sex, suggesting that this asymmetry is neutral with respect to the prediction results.

The present results apply to a treatment-seeking population that is recruited and screened for psychosis risk indicators. The results are not expected to be useful in general population screening. Moreover, the present criteria for a prodromal state reflect emerging clinical symptoms and signs that are thought to be on a continuum with fully psychotic states. Thus, the prediction results apply to a population that is already to some extent ill, rather than to a completely clinically unaffected population, and thus it is more appropriate to view prediction in this context in relation to risk of progression and increasing severity of illness than to the risk of illness per se. It is hoped that the knowledge gained from using this approach to monitor neurobiological changes over time will lead eventually to risk ascertainment criteria that can identify at-risk cases before emergence of subpsychotic clinical features.

The shape of the survival function suggests that the initial 2½ years after ascertainment represents a critical window of opportunity for evaluating changes in brain functioning that may underlie the development of psychosis and for the application of interventions that could attenuate or prevent the emergence of psychotic symptoms and functional disability. The present results thus provide a benchmark for the shape and rate of conversion risk against which to compare in future studies assessing comparable populations provided with a standardized intervention program. The use of prediction algorithms with 80% PPP will

enable more selective recruitment into prevention programs (minimizing exposure of false-positive cases to potential adverse events) and facilitate studies attempting to elucidate neural and other changes proximal to the onset of psychosis.[22,63,64]

Acknowledgments

Funding/Support: This study was supported by investigator-initiated grants from the NIMH and a gift from the Staglin Music Festival for Mental Health.

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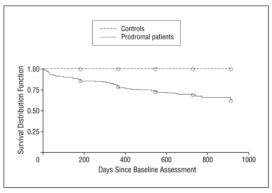

Figure.
Cumulative survival distribution function modeling time to conversion to psychosis in 291 clinical high-risk (prodromal) patients and 134 demographically comparable normal control subjects (dashed line).

Table 1

Sociodemographic Characteristics of the Samples With and Without Follow-up Information Available

Characteristic	Followed Up (n=291)	Not Followed Up (n=79)	Statistic	*df*	*P* Value
Age, mean±SD, y	18.1±4.6	18.6±5.3	t=−0.8	368	.41
Parental education, mean±SD, y	5.4±1.8	4.9±1.9	t=1.7	295	.09
No. of SIPS symptoms, mean±SD					
Positive	12.0±4.1	11.6±3.6	t=0.8	368	.42
Negative	12.1±6.8	11.8±7.1	t=0.3	362	.73
Social functioning, mean±SD score[38]	6.1±1.5	6.3±1.5	t=;0.7	367	.48
Role functioning, mean±SD, score[38]	6.1±1.7	5.9±1.6	t=0.9	368	.33
Global functioning, mean±SD, score[44]	46.5±11.9	45.9±12.6	t=0.4	355	.69
Female, No. (%)	121 (41.6)	20 (25.3)	χ^2=6.9	1	.01
Nonwhite race, No. (%)	56 (19.6)	16 (22.5)	χ^2=3.3	1	.51
Hispanic ethnicity, No. (%)	39 (13.9)	17 (22.7)	χ^2=3.4	1	.07
Entry year, No. (%)			χ^2=8.2	7	.32
1998	16 (5.5)	2 (2.5)			
1999	21 (7.2)	5 (6.3)			
2000	40 (13.8)	7 (8.9)			
2001	35 (12.0)	10 (12.7)			
2002	43 (14.8)	10 (12.7)			
2003	51 (17.5)	11 (13.9)			
2004	70 (24.1)	25 (31.6)			
2005	15 (5.2)	9 (11.4)			
SIPS diagnosis, No. (%)			χ^2=2.0	2	.35
GRD	2 (0.7)	0			
BIPS	7 (2.4)	4 (5.1)			
APS	282 (96.9)	75 (94.9)			
SPD diagnosis, No. (%)	88/287 (30.7)	24/77 (31.2)	χ^2=0.0	1	.94
First-degree relative with psychosis, No. (%)	69/273 (25.3)	14/63 (22.2)	χ^2=0.3	1	.61
First- or second-degree relative with psychosis, No. (%)	118/277 (42.6)	20/64 (31.2)	χ^2=2.8	1	.09

Abbreviations: APS, attenuated positive symptoms; BIPS, brief intermittent psychotic symptoms; GRD, genetic risk and deterioration; SIPS, Structured Interview for Prodromal Syndromes; SPD, schizotypal personality disorder.

Table 2

Potential Predictor Variables by Domain of Assessment

Predictor Domain	No. of Variables	Individual Predictor Variables
Demographics	7	Sex, race, ethnicity, age at baseline, year at baseline,[a] parental education, and study site
Genetic risk	6	Psychosis in first-degree relatives, psychosis in second-degree relatives, psychosis in first- or second-degree relatives, psychosis in first- and second-degree relatives, schizotypal personality disorder, and genetic risk (psychosis in first-degree relatives or schizotypal personality disorder) and functional deterioration (decline of ≥10% in social, role, or psychological functioning in past year)[a]
Positive symptoms	9	Unusual thought content,[a] suspicion/paranoia,[a] disorganized communication,[a] perceptual abnormalities, grandiosity, number of these symptoms rated >2 in severity, number of these symptoms rated >3, number of these symptoms rated >4, and number of these symptoms rated >5
Negative symptoms	10	Avolition, reduced emotional expression, reduced experience of emotion, social anhedonia,[a] reduced ideational richness,[a] reduced occupational functioning, number of these symptoms rated >2 in severity, number of these symptoms rated >3, number of these symptoms rated >4, and number of these symptoms rated >5
Disorganization symptoms	8	Bizarre thinking,[a] difficulties with concentration,[a] odd behavior or appearance, impaired personal hygiene, number of these symptoms rated >2 in severity, number of these symptoms rated >3, number of these symptoms rated >4, and number of these symptoms rated >5
General symptoms	8	Sleep disturbance, dysphoric mood, motor disturbance, impaired tolerance to normal stress,[a] number of these symptoms rated >2 in severity, number of these symptoms rated >3, number of these symptoms rated >4, and number of these symptoms rated >5
Diagnostic comorbidity	12	*DSM-IV* diagnoses of mania, depression, dysthymia, panic disorder, agoraphobia, social phobia, simple phobia, obsessive-compulsive disorder, generalized anxiety disorder, any affective disorder, any anxiety disorder, and any affective or anxiety disorder
Social and role functioning	8	Baseline levels of social functioning,[a] role functioning, psychological functioning, and general functioning[a] and change during the past year in social functioning, role functioning,[a] psychological functioning, and any area of functioning[a]
Substance abuse	8	*DSM-IV* diagnosis of abuse of or dependence on alcohol, hypnotics, cannabis, amphetamines, opiates, cocaine, hallucinogens, or ≥1 of these substances[a]
Antipsychotic drugs	1	Prescription for antipsychotic drugs during the follow-up interval[a]

[a]Indicates that the predictor variable met statistical criteria for screening for association with conversion to psychosis.

Table 3

Multivariate Proportional Hazards Regression Results Within Domains of Predictor Variables

Predictor Domain	Individual Predictor Variables[a]	No. of Patients	χ^2 Test	*P* Value
Demographics	Baseline year	291	9.32	.002
Genetic risk	Psychosis in first-degree relatives with functional decline	291	10.37	.001
Positive symptoms	Unusual thought content	291	7.10	.008
	Suspicion/paranoia	291	7.97	.005
	Disorganized communication	291	10.97	<.001
Negative symptoms	Social anhedonia	287	3.24	.07
	Reduced ideational richness	285	12.21	<.001
Disorganization symptoms	Bizarre thinking	287	8.51	.004
	Difficulties with concentration	286	3.36	.07
General symptoms	Reduced tolerance to stress	286	7.92	.005
Functioning	Social function at baseline	290	8.63	.003
	General function at baseline	281	5.51	.02
	Decline in role functioning in past year	290	3.51	.06
	Decline in social, role, or psychological functioning in past year	290	4.81	.03
Drug abuse	Any drug abuse	270	4.99	.03
Antipsychotic drugs	Antipsychotic drugs during follow-up	287	3.71	.05

[a] No variables in the 7 diagnostic comorbidities domain (Table 2) contributed significantly to psychosis risk.

Arch Gen Psychiatry. Author manuscript; available in PMC 2011 March 28.

Table 4

Prediction Statistics for 5 Uniquely Associated Predictors and Their Combinations

Predictor[a]	No. of Patients	χ^2 Test[b]	*P* Value	Base Rate	Hazard Ratio	PPP	Sensitivity	Specificity
1. Genetic risk with functional decline	291	17.76	<.001	48	1.96	52	66	59
2. Unusual thought content (>3)	291	9.43	.002	43	1.98	48	56	62
3. Suspicion/paranoia (>2)	291	7.59	.006	32	2.12	43	79	37
4. Social functioning (<7)	290	4.99	.03	36	1.79	46	80	43
5. Any substance abuse	270	8.85	.003	20	2.08	43	29	83
1 and 2[c]	291	23.88	<.001	21	3.08	69	38	85
1 and 3[c]	291	23.05	<.001	36	2.93	57	56	72
1 and 4[c]	290	26.39	<.001	33	3.14	61	55	75
1 and 5[c]	270	9.97	.002	10	2.64	41	18	93
2 and 3[c]	291	15.35	<.001	30	2.39	52	45	76
2 and 4[c]	290	10.92	.001	31	2.09	51	44	74
2 and 5	270	7.03	.008	9	2.31	52	17	93
3 and 4[c]	290	19.48	<.001	45	2.83	53	67	63
3 and 5	270	8.18	.004	13	2.29	41	21	90
4 and 5	270	7.26	.007	11	2.23	42	19	91
1, 2, and 3[c]	291	29.27	<.001	18	3.58	74	34	89
1, 2, and 4[c]	290	25.42	<.001	16	3.41	81	30	90
1, 2, and 5	270	9.11	.003	4	3.33	53	10	97
1, 3, and 4[c]	290	30.77	<.001	26	3.43	67	48	82
1, 3, and 5[c]	270	14.05	<.001	7	3.44	51	15	96
1, 4, and 5[c]	270	14.03	<.001	19	3.44	51	15	96
2, 3, and 4[c]	290	19.19	<.001	22	2.72	58	38	84
2, 3, and 5[c]	270	9.85	.002	6	3.26	60	11	96
2, 4, and 5[c]	270	13.88	<.001	6	3.82	62	13	97
3, 4, and 5	270	7.36	.007	9	2.44	46	15	93
1, 2, 3, and 4[c]	290	29.18	<.001	13	3.84	81	28	92

Predictor[a]	No. of Patients	χ^2 Test[b]	*P* Value	Base Rate	Hazard Ratio	PPP	Sensitivity	Specificity
1, 2, 3, and 5[c]	270	15.71	<.001	3	5.53	78	8	98
1, 2, 4, and 5[c]	270	17.11	<.001	4	5.23	67	10	98
1, 3, 4, and 5[c]	270	11.72	<.001	6	3.41	55	13	96
2, 3, 4, and 5[c]	270	12.41	<.001	4	4.12	71	10	97
1, 2, 3, 4, and 5[c]	270	15.71	<.001	3	5.53	79	8	98

Abbreviation: PPP, positive predictive power.

[a]Parenthetical numbers represent the value of the scale exceeded by people who were counted as positive for that indicator.

[b]Significant at a Bonferroni-corrected α of *P*<.002 (.05/26).

[c]Prediction statistics reflect cumulative conversation status at the final follow-up as generated by the Lifetest procedure.[43] The false-positive rate for each predictor is 1-specificity, and the false-negative rate is 1-sensitivity.