A Population-Based Longitudinal Study of Symptoms and Signs Before the Onset of Psychosis

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Objective: The authors sought to characterize the symptoms of patients later hospitalized for psychotic disorders in primary mental health outpatient settings, and to investigate whether these symptoms can be used to predict later onset of psychotic illness.

Method: This was a population-based historical prospective cohort study using national registers of clinical psychiatric services. The sample (N=114,983) comprised 18- to 21-year-olds serving in the Israeli military and examined in military mental health outpatient clinics across 72 consecutive months.

Results: Overall, 1,092 individuals (0.95%) not diagnosed with a psychotic disorder at the time of examination were hospitalized for nonaffective psychotic disorder up to 9 years after the index examination. A principal components analysis of symptoms presented at index examination found that a symptom cluster of thought disorder, perceptual abnormalities, poor orientation, and suicidality was associated with an increased risk for

hospitalization for nonaffective psychotic disorder within 14 days after examination (hazard ratio=45.80, 95% CI=22.87–91.73), 15–111 days after examination, (hazard ratio=19.59, 95% CI=13.08–29.33), 112–365 days after examination (hazard ratio=4.94, 95% CI=2.59–9.40), and 1–3.5 years after examination (hazard ratio=3.42, 95% CI=2.21–5.28), but not for hospitalization 3.5 years or more after examination (hazard ratio=1.57, 95% CI=0.91–2.71). Despite the increased risk, the positive predictive values of this symptom cluster were low, ranging from 0.54% to 1.99%.

Conclusions: In 18- to 21-year-olds, the presence of psychotic symptoms was associated with later hospitalization for a nonaffective psychotic disorder. However, the low positive predictive values of symptoms elicited in primary mental health care settings suggest that symptoms alone are not useful in predicting later hospitalization for nonaffective psychotic disorder.

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The prodrome heralding the onset of a psychotic disorder is commonly defined as the period between the beginning of subtle behavioral and emotional deviations from norms and the clinical manifestation of the full psychotic episode. Prospective studies attempting to identify and predict impending psychosis by following "high-risk" or "prodromal" individuals have proliferated in the past two decades (1–5). (The terms "prodromal" and "ultra high risk" are often used interchangeably; here we use the term "prodromal.") The overwhelming majority of these studies have been conducted in specialized prodromal clinics, to which adolescents arrive via several sequential referral filters (6).

Studies of such samples provide important information on predictors of psychosis and schizophrenia. Significant predictors of nonaffective psychotic disorder found in those settings include genetic risk with recent deterioration in functioning, unusual thought content, suspicion/paranoia, social impairment, history of substance abuse, disorganized symptoms (1, 7, 8), positive

symptoms, bizarre thinking, sleep disturbances, schizotypal disorder, and lower level of education (4). If such findings could be generalized to primary psychiatric care, this would have substantial implications for early detection and early intervention in psychotic disorders.

The aim of this study was to present a population-based context to concepts developed in specialized prodromal clinics. Young men and women examined in military mental health outpatient clinics were followed for psychiatric hospitalizations, and the association between symptoms present at the index examination and risk for later hospitalization for nonaffective psychotic disorders was examined.

This study has two important methodological advantages. First, the 18- to 21-year-olds examined and followed for up to 9 years are representative of the entire population. Second, since mental health care, including hospitalization, is free and easily accessible both in the military and in civilian settings in Israel, biases caused by limited access to mental health care are minimal.

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METHOD

The study was approved by the ethics committees of the Israeli Defense Forces (IDF) Medical Corps and the Chaim Sheba Medical Center.

Service in the IDF is mandatory for all Jewish Israelis between the ages of 18 and 21 for males and 18 and 20 for females. The association between signs and symptoms present in a mental health examination and subsequent psychiatric hospitalization was examined by merging data from the IDF's Mental Health Examination Archive with data from the national Psychiatric Hospitalization Case Registry. These databases were linked using the Israeli national identification number (analogous to the U.S. Social Security number) assigned to all newborns and legal citizens. For service members 18 to 21 years old examined in military mental health outpatient clinics who later appeared in the hospitalization registry, dates of hospitalizations and discharge diagnoses were added to the file. To preserve confidentiality, the national identification number was removed before the linked file was transferred to the investigators.

Databases

IDF Mental Health Examination Archive. The IDF mental health examination archive contains information obtained from military mental health outpatient clinics, including examinations of all young adults serving in the IDF from 2000 to 2006 referred by others or self-referred to mental health examination. These examinations are performed by postgraduate-level licensed social workers, clinical psychologists, or psychiatrists in military mental health outpatient clinics. To achieve the greatest standardization possible, all mental health professionals go through special courses and receive ongoing supervision by senior psychiatrists, psychologists, and social workers, focusing on the administration and documentation of the mental health examination. Referrals to military mental health outpatient clinics are made by military general practitioners, mental health professionals, or commanding officers. The mental health examination consists of a semistructured interview and a structured rating scale documenting the presence or absence of psychiatric signs and symptoms.

Psychiatric Hospitalization Case Registry. The national Psychiatric Hospitalization Case Registry is a complete listing of all psychiatric hospitalizations in Israel, including in psychiatric hospitals, day hospitals, and psychiatric units in general hospitals, using ICD discharge diagnoses assigned by a board-certified psychiatrist. Reporting is regularly monitored to ensure precision.

A study comparing Research Diagnostic Criteria diagnoses with registry diagnoses (9) found that registry diagnoses of nonaffective psychotic disorders (ICD-10 codes F20.0–29.9) had a sensitivity of 0.87, and 93% of patients with schizophrenia in the population are eventually hospitalized and appear in the registry (10).

Study Population

During the years 2000–2006, a total of 114,983 service members 18–21 years old were examined at least once by a mental health professional. Of these, 2,450 (2.1%) were later hospitalized in a psychiatric ward, up to 9 years after the index mental health examination (see Figure S1 in the data supplement that accompanies the online edition of this article). Of those hospitalized, 1,092 received a diagnosis of a nonaffective psychotic disorder (ICD-10 codes F20.0–29.9). These rates of hospitalization for nonaffective psychotic disorder are in agreement with a 2011 report of the Israeli Ministry of Health (25) finding that 58.4% of psychiatric hospitalizations were for the treatment of schizophrenia or other psychotic disorders.

A total of 1,358 service members from the sample were later hospitalized for other psychiatric disorders (2.9% for organic mental disorders [ICD-10 codes F00–F09], 8.1% for substance-related disorders [codes F10–F19], 18.8% for affective disorders [codes F30–F39], 29.7% for anxiety and somatoform disorders [codes F40–F49], 8.0% for eating disorders [code F50], 15.1% for personality disorders [codes F60–F69], 0.2% for intellectual disabilities [codes F70-F79], 0.4% for developmental disorders [codes F80–F89], 4.1% for childhood-onset disorders [codes F90–F98], and 12.7% for unspecified mental disorder [code F99]). The comparison group included 112,533 individuals examined by mental health professionals between 2000 and 2006 who were not later hospitalized in a psychiatric ward.

The nonaffective psychotic disorder group (N=1,092) was classified into five groups according to time from the index mental health examination to hospitalization. The first group comprised those who were hospitalized 0–14 days after the index examination (N=43), an interval suggesting that these individuals may already have been suffering from a psychotic disorder and possibly had been masking their symptoms. Because many prodromal studies have assessed risk for hospitalization within 1 year, we divided those hospitalized between 15 and 365 days according to the median time elapsed between the index examination and later hospitalization, resulting in groups hospitalized between 15 and 111 days (N=143) and between 112 and 365 days (N=138) after the index examination. Individuals who were hospitalized more than 1 year after the examination were also divided according to the median time elapsed between the index examination and later hospitalization, resulting in group hospitalized between 1 and 3.5 years (N=385) and between 3.5 and 9 years after the index examination (N=383).

Statistical Analysis

Cox proportional hazards regression models were used to compare the prevalence of individual symptoms identified in the first mental health examination between individuals who were later hospitalized for a nonaffective psychotic disorder, those later hospitalized for other psychiatric disorders, and those who were not later hospitalized for a psychiatric disorder. Hazard ratios with 95% confidence intervals were computed.

In an attempt to classify clinically recognizable symptom clusters, we clustered the 24 symptoms recorded during the index mental health examination into clusters using categorical

principal components analysis with variable principal normalization. These clusters were then dichotomized, such that individuals with at least one of the symptoms in a given cluster were included in that cluster and compared with those not having any of the symptoms in the cluster. The dichotomized cluster scores were then included in a Cox proportional hazards regression analysis to assess which cluster of symptoms best predicted later hospitalization, followed by analyses stratified by time from examination. We then performed a "high-risk group" analysis, examining the potential additive effects of the presence of other symptom clusters in addition to symptoms from the psychotic symptom cluster. Hazard ratios with 95% confidence intervals were computed. The sensitivity, specificity, and positive predictive values were calculated for each category of symptoms.

Analyses were performed using SPSS, version 17.0 (SPSS, Inc., Chicago).

RESULTS

Psychiatric Symptoms in 18- to 21-Year-Olds
Table 1 presents the prevalence of each individual symptom present in the index mental health examination among service members 18–21 years old who were later hospitalized for non-affective psychotic disorders, those who were later hospitalized for other psychiatric disorders, and those who were not later hospitalized. Service members examined in the military mental health clinics presented with between zero and six symptoms. Those who were later hospitalized for nonaffective psychotic disorders or other psychiatric disorders reported significantly more symptoms than those not later hospitalized ($p \leq 0.001$).

Principal Components Analysis
Nominal categorical principal components analysis to cluster all symptoms identified four clusters (Table 2): 1) depressive symptoms (negative affect, depressed mood, disturbance of sleep, reduced appetite, anxiety, disheveled appearance and abnormal behavior, and suicidal ideation; 2) risk behavior and impulse control problems (impulse control problems, aggressive behavior, and impaired judgment); 3) psychotic symptoms (thought disorder, perceptual abnormalities, poor orientation, and previous suicide attempts); 4) other symptoms (social isolation, emotional lability, poor self-esteem, and substance abuse). Sexual orientation problems, obsessive-compulsive behavior, memory problems, somatic problems, sexual dysfunction, and enuresis did not load on any cluster (loadings <0.3) and therefore were not included in the final principal components analysis. Each cluster had an eigenvalue >1, and the total variance accounted for was 29.95%. Although this value may seem low, a smaller proportion of explained variance is expected when categorical variables are used in principal components analysis (11).

Risk of Hospitalization for Nonaffective Psychotic Disorder After Index Mental Health Examination
The risk of hospitalization for a nonaffective psychotic disorder was elevated for the entire duration of follow-up among individuals who presented with psychotic symptoms (hazard ratio=5.37, 95% CI=4.36–6.61; follow-up mean=5.3 years, median=5.2 years, range=0–9.3 years) (Table 3). However, the association between psychotic symptoms and hospitalization attenuated over time. In individuals hospitalized within 14 days, the hazard ratio was 45.80 (95% CI=22.87–91.73), and it decreased to 1.57 (95% CI=0.91–2.71) in those who were hospitalized 3.5 years or more after the index examination. Sensitivity similarly decreased from 48.84% for the group hospitalized within 14 days to 3.66% for the group hospitalized 3.5 years or more after the index examination. The specificity was 98.20%. The positive predictive values of this cluster ranged from 0.54% to 1.99%. Among those who presented with thought disorder or perceptual abnormalities, the risk of hospitalization for a nonaffective psychotic disorder for the entire duration of follow-up relative to the nonhospitalized comparison group was sixfold higher (hazard ratio=6.09, 95% CI=4.20–8.83).

The risk of later hospitalization for a nonaffective psychotic disorder was also increased for the entire duration of follow-up among individuals who presented with risk behavior and impulse control problems, as it was for those who presented with social isolation, emotional lability, poor self-esteem, and substance abuse (hazard ratio=2.25, 95% CI=1.76–2.88, and hazard ratio=1.44, 95% CI=1.21–1.70, respectively) (Table 3). In contrast, depressive symptoms were associated with a lower risk for hospitalization for a nonaffective psychotic disorder for the entire duration of follow-up (hazard ratio=0.77, 95% CI=0.68–0.87) (Table 3).

In the subanalysis performed on the high-risk group of individuals who presented with psychotic symptoms at the first mental health examination, the presence of symptoms from the impulse control and risk behavior problems cluster (hazard ratio=3.64, 95% CI=2.33–5.68) or other symptoms (hazard ratio=1.70, 95% CI=1.17–2.47) was associated with an elevated risk for hospitalization for a nonaffective psychotic disorder for the entire follow-up period.

Risk of Hospitalization for Other Psychiatric Disorders After Index Mental Health Examination
The risk of hospitalization for other psychiatric disorders during the entire follow-up period was elevated among individuals who presented with psychotic symptoms (hazard ratio=3.14, 95% CI=2.25–4.38), impulse control and risk behavior problems (hazard ratio=2.04, 95% CI=1.42–2.95), or symptoms from the other symptoms cluster (hazard ratio=1.46, 95% CI=1.17–1.183). Analyses stratified by time from index examination were also conducted, utilizing the same groups as for hospitalization for nonaffective psychotic disorders (Table 1; see also the online data supplement). The association between psychotic symptoms or impulse control and risk behavior problems and hospitalization attenuated over time, with a pattern similar to that observed for hospitalization for nonaffective psychotic disorders, although the strength of the associations were slightly lower.

TABLE 1. Prevalence of Symptoms Among 18- to 21-Year-Olds and Association With Risk of Later Hospitalization for Nonaffective Psychotic Disorder or for Other Psychiatric Disorders

Symptom	A Hospitalized for Nonaffective Psychotic Disorder (%) (N=1,092)	B Hospitalized for Other Psychiatric Disorders (%) (N=1,358)	C Not Hospitalized for Psychiatric Disorders (%) (N=112,533)	A vs. B (ref.) Hazard Ratio	A vs. B (ref.) 95% CI	A vs. C (ref.) Hazard Ratio	A vs. C (ref.) 95% CI	B vs. C (ref.) Hazard Ratio	B vs. C (ref.) 95% CI
Negative affect	28.2	31.0	28.3	0.89	0.76–1.05	0.92	0.77–1.06	0.98	0.82–1.17
Depressed mood	19.1	22.1	24.6	0.99	0.83–1.18	0.78	0.65–0.93	0.89	0.74–1.08
Disturbance of sleep	12.9	15.6	16.6	0.91	0.73–1.12	0.78	0.63–0.96	0.93	0.75–1.16
Reduced appetite	8.5	12.9	11.9	1.04	0.82–1.31	0.84	0.67–1.07	1.04	0.82–1.32
Anxiety	17.3	18.8	17.5	0.92	0.76–1.12	0.91	0.75–1.10	1.02	0.83–1.26
Disheveled appearance and abnormal behavior	9.7	8.7	5.2	1.30*	1.02–1.66	1.94	1.52–2.48	1.59	1.19–2.13
Suicidal ideation	7.1	11.8	5.8	0.73*	0.55–0.97	1.17	0.88–1.55	1.92	1.48–2.47
Emotional lability	11.4	8.9	6.6	1.24	0.97–1.59	1.57	1.22–2.00	1.31	0.97–1.75
Social isolation	5.8	4.7	3.9	0.96	0.72–1.28	1.74	1.31–2.33	1.47	1.04–2.08
Previous suicide attempt	1.9	3.5	1.2	0.53*	0.30–0.94	1.23	0.70–2.18	3.00	1.99–4.51
Impulse control problems	2.6	2.7	1.3	0.76	0.49–1.18	1.86	1.19–2.90	2.48	1.62–3.80
Aggressive behavior	2.7	1.2	1.1	1.25	0.81–1.90	2.50	1.64–3.83	1.51	0.83–2.74
Substance abuse	1.7	1.5	0.5	1.19	0.96–2.16	2.75	1.52–4.99	2.79	1.45–5.39
Thought disorder	6.6	2.7	0.5	2.96*	2.02–4.35	7.39	5.03–10.85	3.26	1.74–6.08
Perceptual abnormalities	1.6	0.9	0.2	0.51	0.13–2.05	1.51	0.38–6.05	5.43	2.43–12.12
Obsessive-compulsive behavior	2.3	2.1	0.9	1.18	0.70–2.00	2.11	1.25–3.58	2.41	1.39–4.18
Impaired judgment	2.5	1.2	0.2	3.00*	1.61–5.60	5.87	3.14–10.95	2.81	1.05–7.52
Poor orientation	1.1	0.3	<0.1	3.22*	1.04–10.02	13.68	4.40–42.52		
Memory problems	0.7	0.7	0.2	2.68*	1.00–7.16	2.69	1.01–7.18	1.64	0.41–6.58
Sexual orientation problems	1.1	0.1	0.3	2.03*	1.09–3.80	4.10	2.20–7.65	0.50	0.07–3.53
Sexual dysfunction	0.5	0.5	0.4	1.93	0.62–5.99	0.94	0.30–2.92	1.15	0.37–3.56
Poor self-esteem	2.3	3.0	2.1	0.74	0.46–1.20	1.10	0.68–1.77	1.76	1.15–2.69
Somatic problems	2.1	2.2	2.4	0.82	0.49–1.37	0.79	0.47–1.31	1.15	0.72–1.84
Enuresis	0.5	0.8	1.2	0.49	0.20–1.18	0.51	0.21–1.23	0.99	0.49–1.99

*p<0.05.

DISCUSSION

In this study of a population-based sample of 18- to 21-year-olds, the strongest predictor of hospitalization for a nonaffective psychotic disorder was the presence of a cluster of symptoms including thought disorder, perceptual abnormalities, poor orientation, and suicidality at the time of the index mental health examination. These results confirm previous findings, from studies conducted both in specialized prodromal clinics (4, 7) and in the general population (12, 13), that subthreshold psychotic symptoms are associated with an elevated risk for later developing a psychotic disorder. The results further support the focus of prodromal clinics on individuals with attenuated psychotic symptoms, as this

TABLE 2. Categorical Principal Components Analysis of Symptoms in 18- to 21-Year-Olds[a]

Symptom	Depressive Symptoms	Risk Behavior and Impulse Control Problems	Psychotic Symptoms	Other Symptoms
Negative affect	0.55			−0.30
Depressed mood	0.52			−0.38
Disturbance of sleep	0.58			−0.41
Reduced appetite	0.48			−0.46
Anxiety	0.36			
Disheveled appearance and abnormal behavior	0.47			0.24
Suicidal ideation	0.41		0.26	
Impulse control problems		0.54		0.39
Aggressive behavior	0.21	0.54	0.20	0.41
Impaired judgment		−0.41		0.25
Previous suicide attempts	0.24		0.37	
Thought disorder	0.23	−0.24	−0.44	0.31
Perceptual abnormalities		−0.46	0.55	
Poor orientation		−0.38	0.54	
Social isolation	0.33			0.35
Emotional lability	0.38			0.38
Poor self-esteem		−0.25		0.36
Substance abuse				0.39
Sexual orientation problems	0.24	−0.26	0.26	0.25
Obsessive-compulsive behavior		−0.29	−0.25	
Memory problems			−0.24	
Somatic problems		0.23	−0.28	
Sexual dysfunction				
Enuresis				
Eigenvalue	2.39	1.53	1.45	1.82
% of variance	9.94	6.38	6.04	7.60

[a] Only loadings ≥0.2 are presented.

study shows that even within primary mental health care settings, this group had the greatest risk for later hospitalization for nonaffective psychotic disorders. We also found that risk behavior and impulse control problems were associated with later hospitalization for nonaffective psychotic disorders. This is in agreement with previous reports of behavioral and emotional instability, impulsivity, and problems with aggression control before the clinical onset of psychotic disorders (14–16).

Depressive symptoms were associated with lower risk for hospitalization for nonaffective psychotic disorder. Some studies have reported that depression is highly prevalent in the prodromal phase of psychotic illness (2), and it has been found to be predictive of psychotic disorder in prodromal individuals (5) and in individuals in the general population presenting with hallucinations (17), while other studies did not find dysphoric mood to contribute uniquely to psychosis prediction (7) or suggested that depression before the onset of the first psychotic episode was more strongly associated with a later diagnosis of an affective psychosis than with a later diagnosis of schizophrenia (18).

The North American Prodrome Longitudinal Study (7) reported a positive predictive value of 52% for prodromal patients with higher levels of unusual thought content and suspicion/paranoia, and positive predictive values between 68% and 80% for prediction algorithms combining two or three of the following: genetic risk for schizophrenia,

deterioration in functioning, unusual thought content, suspicion/paranoia, social impairment, and a history of substance abuse. The prospective European Prediction of Psychosis Study (4) predicted transition to psychosis using positive symptoms, bizarre thinking, sleep disturbances, a schizotypal disorder, past-year level of functioning, and years of education; that model had a positive predictive value of 83.3%. A meta-analysis of the prediction ability of prodromal clinical interview instruments for later active psychosis showed very good predictive power in help-seeking individuals but not in the general population, with a reported positive predictive value of 5.7% (19). Our population-based study yielded positive predictive values that are at the lower range of the latter estimate, in particular within the first 111 days after first examination. Those hospitalized within 2 weeks of the index mental health examination had a hazard ratio of 45 for psychotic symptoms, suggesting that these adolescents were probably already acutely psychotic, hence were hospitalized within days, and probably should have been diagnosed as suffering from a psychotic disorder at their examination. As time to hospitalization increased, the predictive ability of psychotic symptoms decreased gradually, as is expected. In psychotic illness, psychotic symptoms usually appear at low intensity and gradually increase over time until reaching a threshold enabling diagnosis (7).

The lower positive predictive value in population-based settings compared with prodromal clinics is likely due to the

TABLE 3. Risk for Hospitalization for a Nonaffective Psychotic Disorder Using Clusters From Principal Components Analysis, Including Positive Predictive Value (PPV), Sensitivity, and Specificity, by Interval From Index Mental Health Examination to Hospitalization

	Cluster							
	Depressive Symptoms		Risk Behavior and Impulse Control Problems		Psychotic Symptoms		Other Symptoms	
Measure	Statistic	95% CI	Statistic	95% CI	Statistic	95% CI	Statistic	95% CI
Hospitalization for nonaffective psychotic disorder during entire duration of follow-up								
Hazard ratio	0.77	0.68–0.87	2.25	1.76–2.88	5.37	4.36–6.61	1.44	1.21–1.70
PPV	0.93	0.86–1.02	2.7	2.13–3.41	1.01	0.83–1.20	1.47	1.27–1.70
Sensitivity	48.9	45.90–51.91	19.57	15.10–24.70	5.15	4.27–6.20	17.12	14.96–19.52
Specificity	49.94	49.65–50.24	97.73	97.64–97.81	98.2	98.12–98.28	88.86	88.67–89.04
Hospitalization for nonaffective psychotic disorder 1–14 days from index examination								
Hazard ratio	0.49	0.25–0.94	4.48	2.06–9.77	45.8	22.87–91.73	2.45	1.25–4.79
PPV	0.04	0.02–0.06	0.35	0.17–0.69	1.03	0.65–1.59	0.13	0.08–0.22
Sensitivity	55.81	40.01–70.59	20.93	10.58–36.48	48.84	33.56–64.32	39.53	25.37–55.55
Specificity	49.94	49.65–50.24	97.73	97.64–97.81	98.2	98.12–98.28	88.86	88.67–89.04
Hospitalization for nonaffective psychotic disorder 15–111 days from index examination								
Hazard ratio	0.77	0.54–1.10	2.84	1.63–4.96	19.59	13.08–29.33	1.64	1.09–2.46
PPV	0.14	0.11–0.18	0.58	0.34–0.98	1.99	1.45–2.71	0.29	0.20–0.49
Sensitivity	56.64	48.10–64.82	10.49	6.19–17.00	28.67	21.58–36.93	25.17	18.47–33.25
Specificity	49.94	49.65–50.24	97.73	97.64–97.81	98.2	98.12–98.28	88.86	88.67–89.04
Hospitalization for nonaffective psychotic disorder 112–365 days from index examination								
Hazard ratio	0.66	0.46–0.94	1.6	0.69–3.69	4.94	2.59–9.40	1.52	0.95–2.44
PPV	0.11	0.08–0.14	0.24	0.01–0.54	0.54	0.28–0.99	0.18	0.12–0.28
Sensitivity	44.2	35.84–52.89	4.35	1.78–9.63	7.92	4.24–14.15	16.67	11.07–24.17
Specificity	49.94	49.65–50.24	97.73	97.64–97.81	98.2	98.12–98.28	88.86	88.67–89.04
Hospitalization for nonaffective psychotic disorder 1–3.5 years from index examination								
Hazard ratio	0.77	0.62–0.95	2.57	1.67–3.93	3.42	2.21–5.28	1.22	0.90–1.64
PPV	0.32	0.27–0.36	0.93	0.60–1.04	1.12	0.73–1.70	0.44	0.34–0.58
Sensitivity	46.49	41.44–51.62	6.23	4.12–9.26	5.97	3.91–8.96	14.55	11.26–18.56
Specificity	49.94	49.65–50.24	97.73	97.64–97.81	98.2	98.12–98.28	88.86	88.67–89.04
Hospitalization for nonaffective psychotic disorder ≥3.5 years from index examination								
Hazard ratio	0.69	0.39–1.18	1.55	0.95–2.56	1.57	0.91–2.71	1.47	1.09–1.99
PPV	0.33	0.29–0.39	0.66	0.40–1.08	0.69	0.39–1.18	0.44	0.33–0.57
Sensitivity	49.35	44.24–54.47	4.44	2.69–7.15	3.66	2.09–6.20	14.36	11.09–18.37
Specificity	49.94	49.65–50.24	97.73	97.64–97.81	98.2	98.12–98.28	88.86	88.67–89.04

fact that patients often arrive at prodromal clinics after consecutive stages of screening, e.g., first being examined by a school psychologist or a family physician, then being referred to a general psychiatrist, and only then being referred to a specialized prodromal clinic. The psychopathology in patients assessed in prodromal clinics is substantial (20), and these patients are very different from 18- to 21-year-olds presenting at a military mental health outpatient clinic. As military service in Israel is mandatory, soldiers represent the general population in Israel in the 18- to 21-year age range and hence are, we believe, comparable to individuals seeking treatment at a college mental health clinic. The nature of our study population, representative of the general population, may be a possible explanation for the clusters including symptoms that do not seem to fit together. For example, "psychotic symptoms" include poor orientation and suicide attempts, and the cluster "other symptoms" includes a mixture of clinical features that appear unrelated to each other (sexual orientation, self-esteem, substance abuse, obsessive-compulsive behavior). These results reflect the empirical clustering of symptoms in this general population cohort, and they probably reflect the heterogeneity of this sample, as opposed to the more homogeneous population of high-risk prodromal patients.

We found a significant association between the presence of psychotic symptoms and hospitalization for other psychiatric disorders, although to a lesser magnitude than for hospitalization for nonaffective psychotic disorders. This is in agreement with previous work reporting that two-thirds of individuals classified as high risk will not convert to full psychotic disorder, with the majority of these individuals experiencing nonpsychotic disorders (21).

To our knowledge, this is the first study on symptoms associated with the psychosis prodrome that is population-based and uses a prospective, albeit historical, design. We know of only one other population-based study on the topic,

the seminal ABC Schizophrenia Study (2, 22). That study, however, collected data retrospectively and compared case subjects with healthy comparison subjects. The overwhelming majority of previous prospective studies on the prodrome have focused on highly selected patients with diagnostic uncertainty or persons already manifesting mild psychotic symptoms at the time of referral (23).

This study has several important strengths. First, the military has little tolerance for odd behaviors, which leads to a low threshold for referral to a mental health examination. Our sample therefore may include case subjects who would not necessarily seek medical attention or might not be referred for psychiatric consultation in a community setting. Second, the national Psychiatric Hospitalization Case Registry lists all psychiatric hospitalizations in Israel. Therefore, this study has little loss to follow-up, in contrast to studies from prodromal clinics, which are prone to loss to follow-up. In addition, we were able to follow these individuals for a prolonged period, up to 9 years, to verify hospitalization for psychotic disorder.

Nevertheless, limitations of the study should be acknowledged. Our sample did not include individuals with very poor functioning in adolescence, as they are not drafted into the IDF. Also, the military mental health examination is a standard clinical examination without a formal assessment for prodromal symptoms. Nevertheless, many of the symptoms that appear in prodrome questionnaires, such as the Structured Interview for Prodromal Symptoms and the Scale of Prodromal Symptoms (24), are included in the interviews conducted by military mental health professionals, including unusual thought content, subthreshold perceptual abnormalities, social isolation, and sleep disturbance. It is possible that if an instrument specifically aimed at identifying prodromal symptoms had been administered to all 18- to 21-year-olds, more of the future patients would have been identified. In addition, some individuals might have been treated successfully as outpatients and hence avoided hospitalization.

In summary, among 18- to 21-year-olds in a general population setting, the presence of psychotic symptoms was associated with later hospitalization for a nonaffective psychotic disorder. However, the positive predictive value of these symptoms was very low. The clinical setting of this study, characterized by a low threshold and high sensitivity to odd and unusual behaviors, and use of a population-based sample performing mandatory military service, coupled with free access to health care, point to the challenges of applying prediction algorithms or risk calculators (20) outside the context of the specialized prodromal clinics in which they were developed.

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