

ONLINE FIRST

Self-reported Attenuated Psychotic Symptoms as Forerunners of Severe Mental Disorders Later in Life

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Context: It has been suggested that attenuated psychotic symptoms (APSS) reported by people who do not have psychotic disorders signal risk for later severe mental illness.

Objective: To investigate this suggestion using follow-up assessments of hospitalization for clinical diagnoses of nonaffective psychotic and other psychiatric disorders.

Design: Longitudinal cohort study of self-reported APSS with outcome assessment of severe mental illness obtained through linkage with a national hospitalization case registry.

Setting: Israel.

Participants: A stratified full probability sample of 4914 persons aged 25 to 34 years who were screened for psychopathology in the 1980s.

Main Outcome Measure: Subsequent psychiatric hospitalization was ascertained using the psychiatric hospitalization registry, with a mean follow-up of 24 years.

Results: After removing subjects with diagnosable psychotic disorders at baseline, 57.2% of the remaining sample reported at least 1 weak (infrequent) APS and 14.3% reported at least 1 strong (frequent) APS in the year preceding the assessment. Self-reported APSS predicted risk of later hospitalization for nonaffective psychotic disorders, mostly during the 5 years after baseline (adjusted odds ratio = 4.31; 95% CI, 2.21-8.41; positive predictive value = 1.27%; population attributable risk fraction = 33%). Also, APSS increased the risk of later hospitalization for other psychiatric disorders, albeit to a lesser extent (adjusted odds ratio = 2.21; 95% CI, 1.02-4.82).

Conclusions: Self-reported APSS signal risk for later nonaffective psychotic disorders but are not clinically useful as predictors. The difference between these population-based data and the high-risk literature in terms of the positive predictive value (1% vs 10%, respectively) and the time window of transition (5 years vs 12 months, respectively) can be attributed to the selective enrichment strategies that produce high-risk samples.

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IT HAS LONG BEEN RECOGNIZED that schizophrenia-like pathology is also expressed at attenuated levels in individuals with schizotypal or schizoid personality traits,¹ and mild attenuated paranoid delusional thinking and auditory hallucinations are observed in up to 30% of the general population.² There is consistent evidence that these attenuated psychotic symptoms (APSS) may be construed as an expression of liability for schizophrenia and related disorders,³⁻⁹ just as higher but borderline abnormal levels of blood pressure or glucose express higher liability for metabolic and cardiovascular disease.¹⁰ This interpretation is supported by studies showing a link between APSS and nonaffective psychotic^{3,11-14} and, to a lesser extent, other psychiatric disorders.^{15,16}

Doubt may be expressed about the validity of these findings, however, as the measurements of psychotic disorders at follow-up in these studies were mostly based on lay-interviewer assessments using instruments such as the Composite International Diagnostic Interview,¹⁷ which is not an optimal instrument for the diagnosis of psychotic disorders.¹⁸⁻²⁰ As hospitalization is a more conservative outcome measure, we assessed clinical outcomes of self-reported APSS during 24 years by linkage to a nationwide psychiatric hospitalization case registry,^{21,22} hence reducing the possibility of false-positive outcomes. We hypothesized the following: (1) APSS would be strongly associated with an increased risk of later hospitalization for nonaffective psychotic disorder; (2) this association would be pres-

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ent but weaker for other psychiatric hospitalizations; and (3) APs would interact with social functioning, major depressive disorder, anxiety, exposure to trauma, and cannabis use^{11,13,23-28} in models predicting risk of later hospitalization for nonaffective psychotic disorders.

METHODS

The association between APs and subsequent psychiatric hospitalization was examined by merging data from an epidemiological study conducted in Israel in the 1980s with data from the National Psychiatric Hospitalization Case Registry. After receiving approval from the local ethics committee, these databases were linked in 2007 using the national identification number (analogous to the US Social Security number) as the linking variable. For subjects who participated in the epidemiological study and appeared in the hospitalization registry, dates of hospitalizations and discharge diagnoses were added to the file. Individuals who had a discharge diagnosis of nonaffective psychotic disorder (*International Statistical Classification of Diseases, 10th Revision [ICD-10]* codes F20.0-F29.9) at any hospitalization were considered clinically diagnosed as having a psychotic disorder.

To preserve subjects' confidentiality, the national identification number was removed before the linked file was transferred to the investigators.

EPIDEMIOLOGICAL STUDY

This study used data from a 2-stage epidemiological study of mental disorders among young adults in a 10-year birth cohort (1949-1958) conducted in Israel in the 1980s.^{29,30} As part of the original study's goal to compare the risk of selected disorders in socioeconomically contrasting ethnic groups, a sample of 19 000 Israel-born individuals was drawn from the population registry and screened for father's continent of origin (North Africa or Europe) and level of education. This was done to balance socioeconomic status within advantaged and disadvantaged ethnic groups by oversampling disadvantaged subjects from North African origin with high educational level and advantaged subjects of European origin with low educational level. Based on sex, education, ethnicity, and year of birth, 5200 subjects were selected.

This sample was screened and diagnosed for psychotic and other psychiatric disorders in 2 stages. During the screening stage, 4914 subjects (94.5%) were interviewed using a Hebrew version of the Psychiatric Epidemiology Research Interview (PERI), a well-validated screening tool.^{26,31,32} Data were not obtained for 286 subjects (5.5%). Of these, approximately 2.0% had already been hospitalized for schizophrenia at least once; 160 (2.4%) died after age 15 years, of whom approximately 2.5% had been hospitalized for schizophrenia. An additional 334 subjects (6.4%) had migrated and data regarding psychiatric illness were unavailable. The mean (SD) age at the time of the interview was 29.4 (3.1) years; 49.6% were men. Subjects reaching predetermined cutoff values on the PERI,²⁶ unable to complete the screening interview, or suspected of having a history of psychiatric illness were referred for a clinical diagnostic (second) stage (n=2643) along with 416 of the "negatives" from the first stage to control for false-negatives. From this subsample, 2741 subjects (90.8%) were interviewed by psychiatrists using a modified lifetime version of the Schedule for Affective Disorders and Schizophrenia-Israel to arrive at a Research Diagnostic Criteria (RDC)³³ diagnosis. The Schedule for Affective Disorders and Schizophrenia-Israel also included an assessment of the best level of social functioning during the 5

years preceding the interview, rated on a scale of 1 (superior) to 7 (grossly inadequate). The mean (SD) time from the screening stage (PERI) to the second stage (Schedule for Affective Disorders and Schizophrenia-Israel) was 1.1 years (11.5 months) (range, 0-4.5 years).

SELF-REPORTED APs

Self-reports of APs were assessed using the 13-item false beliefs and perceptions subscale of the PERI. Subjects were asked whether they had experienced APs, and the frequency of each symptom during the past year was recorded on a 5-item Likert scale with the following scores: 0 indicates never; 1, rarely; 2, sometimes; 3, often; and 4, very often. The scale includes questions assessing core APs such as delusions, hallucinations, and bizarre thinking; feeling possessed; feeling dissolved; feeling that thoughts are not one's own; and beliefs of mind control. An example of a typical question is, "Have you felt that your mind was dominated by external forces that you had no control over?" The PERI false beliefs and perceptions subscale is based on criteria similar to that of the CIDI psychosis section (version 1.1), the favored instrument in similar studies^{13,23,34,35} (eAppendix and eTable 1, <http://www.archgenpsychiatry.com>). The PERI screening scales, including the false beliefs and perceptions subscale, were tested for reliability and criterion validity and were calibrated against known cases of psychiatric disorders in a pilot research project in Israel.²⁶

NONSPECIFIC PSYCHOLOGICAL DISTRESS

Nonspecific psychological distress was assessed using the PERI demoralization subscale,³⁶ which includes 27 items drawn from 8 subscales: anxiety, sadness, psychophysiological symptoms, perceived physical symptoms, low self-esteem, hopelessness or helplessness, confused thinking, and dread. Each symptom is scored on a 5-point Likert scale, ranging from a score of 0, indicating never or not at all like you, to a score of 4, indicating very often or very much like you. The total score is obtained by calculating the mean of the 27 items. In the analyses, a dichotomous variable split around the median value of the distribution was used.

BASELINE DIAGNOSES OF NONAFFECTIVE PSYCHOTIC DISORDERS, ALCOHOLISM, MAJOR DEPRESSIVE DISORDER, AND ANXIETY DISORDERS

Psychiatric diagnoses of RDC-probable and RDC-definite disorders³⁷ were taken from the second stage of the study.^{30,33} These included nonaffective psychotic disorders (including schizophrenia), alcoholism, major depressive disorder, and anxiety disorders (including panic disorder, generalized anxiety disorder, obsessive-compulsive disorder, and phobic disorder).

CANNABIS USE

Lifetime use of cannabis (including single or rare use) was recorded based on self-report in the screening interview. Subjects were asked whether they had ever used marijuana or hashish. Answers were coded as yes or no.

EXPOSURE TO TRAUMA

Self-report of exposure to trauma was based on data from the screening stage. This included self-report of exposure to war or terrorism or having been a prisoner of war.

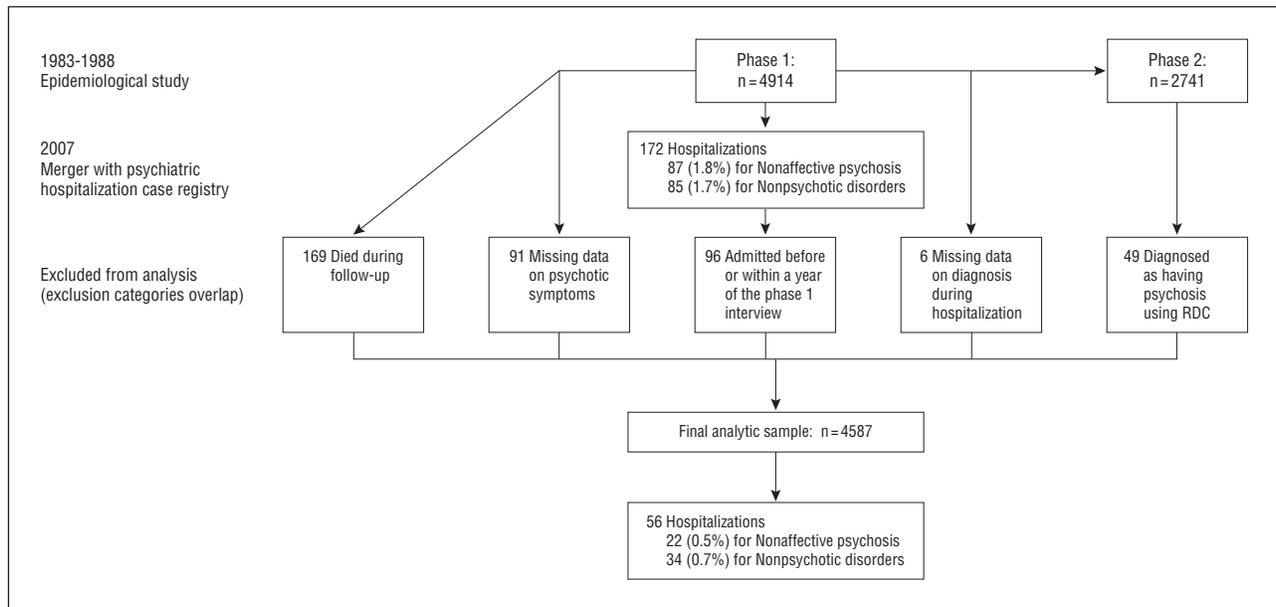


Figure 1. Study population. RDC indicates Research Diagnostic Criteria.

NATIONAL PSYCHIATRIC HOSPITALIZATION CASE REGISTRY

The National Psychiatric Hospitalization Case Registry^{21,22} is a complete listing of all psychiatric hospitalizations in the country, including 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 accuracy. A study comparing RDC diagnoses with registry diagnoses found that the sensitivity of the registry diagnosis of nonaffective psychotic disorders was 0.89, and that of schizophrenia was 0.87.^{21,22}

STUDY POPULATION

Of the 4914 subjects who participated in the screening interview, 172 had a subsequent psychiatric hospitalization, 87 (1.8%) of whom were hospitalized at least once for a nonaffective psychotic disorder (ICD-10 codes F20.0-F29.9). During the follow-up, 169 cohort members had died and were thus excluded from the analysis. In addition, we removed the following subjects from the analyses: (1) those with missing data on the PERI false beliefs and perceptions subscale; (2) those diagnosed as having a psychotic disorder during the Schedule for Affective Disorders and Schizophrenia–Israel interview; (3) those hospitalized in psychiatric facilities prior to or within a year after the PERI assessment (and hence might have been in the prodromal stages of their first psychotic episode); and (4) those with missing data on diagnosis from the hospitalization registry (**Figure 1**). The final sample included 4587 subjects.

During the follow-up period (mean [SD] time from PERI interview to first hospitalization or to date of merger in 2007, 23.8 [1.9] years), 22 individuals (0.5%) were identified in the National Psychiatric Hospitalization Case Registry as having been later hospitalized at least once for a nonaffective psychotic disorder (ICD-10 codes F20.0-F29.9; including diagnoses of schizophrenia [n=15], schizoaffective disorder [n=4], and psychotic disorder not otherwise specified [n=3]). The reason for this relatively low rate of nonpsychotic disorders (0.5%) in the analytic sample is that most subjects with these disorders had already manifested their illness at the time of the epidemiological study and hence were excluded from this analy-

sis, which focuses on the risk associated with APSs in subjects not diagnosed as having a concurrent psychotic illness. Thirty-four subjects (0.7%) were identified as having been hospitalized for other disorders, including drug use, personality disorders, affective disorders, anxiety disorders, and organic mental disorders.

STATISTICAL ANALYSIS

All analyses were performed using Stata version 10 statistical software (StataCorp LP). The data were weighted to estimate the rates of APSs in the original population from which the cohort sample was drawn. All numbers shown represent the actual number of subjects, whereas the percentages are weighted.

To assess the effect of baseline reports of APSs on later hospitalization, we created a mean APS score for each subject (for more details, see the eAppendix). We examined whether this mean APS score was influenced by age, origin, marital status, and other demographic variables. The mean APS score was then used in a logistic regression model to predict later hospitalization for nonaffective psychotic and other psychiatric disorders. In the next step, a logistic regression analysis looking at the presence of any APS in the past year and risk of later hospitalization for a nonaffective psychotic or other psychiatric disorder was performed.

As in previous studies,^{12,14,34} separate scores were defined for weak (occurring rarely or sometimes) and strong (occurring often or very often) APSs. Logistic regression analyses were performed to examine the association between no APSs (n=1187), weak APSs (n=2595), or strong APSs (n=766) at baseline and hospitalization for nonaffective psychotic or other psychiatric disorders by 2007. Associations were expressed as odds ratios (ORs)³⁸ and 95% CIs, presented before and after adjustment for age, sex, education, and ethnicity.

To examine linear effects, the number of weak or strong APSs was then entered into logistic regression analyses examining their association with hospitalization for nonaffective psychotic or other psychiatric disorders.

The population attributable fraction, or the proportion of admissions that could be prevented if APSs were removed from the population assuming causality, was calculated from the OR, ie, $[(OR - 1)/OR] \times \text{prevalence of exposure in the cases}$,³⁹ as were

Table 1. Distribution of Mean Ratings of Psychotic Experiences According to Demographic Variables

Variable	PERI False Beliefs and Perceptions Subscale Score, Mean (SD)	F Score	P Value	No. (%) ^a		χ^2 Statistic	P Value
				Any Weak Experience	Any Strong Experience		
Sex		0.4	.52			6.7	.03
Male	0.26 (0.32)			1308 (58.9)	389 (14.4)		
Female	0.27 (0.36)			1309 (55.6)	389 (14.3)		
Ethnicity		163.0	<.001			91.8	<.001
European	0.22 (0.29)			1315 (58.2)	260 (11.3)		
North African	0.36 (0.41)			1302 (55.2)	518 (21.3)		
Cannabis use		73.1	<.001			61.6	<.001
No	0.25 (0.33)			2212 (56.1)	628 (13.5)		
Yes	0.38 (0.39)			405 (64.8)	150 (20.4)		
Marital status		76.8	<.001			51.8	<.001
Married	0.24 (0.32)			2059 (56.6)	571 (13.1)		
Unmarried	0.36 (0.39)			547 (59.7)	205 (20.7)		
Employment status		18.1	<.001			21.1	<.001
Employed	0.26 (0.33)			2467 (57.7)	696 (13.8)		
Unemployed	0.36 (0.44)			150 (48.4)	82 (24.6)		
Age ^b		24.5	<.001			14.5	.001
≤Median	0.30 (0.36)			1488 (57.9)	484 (16.2)		
>Median	0.24 (0.32)			1112 (57.0)	282 (13.0)		

Abbreviation: PERI, Psychiatric Epidemiology Research Interview.

^aWeak indicates those who reported at least 1 psychotic experience rarely or sometimes but never fairly often or very often; strong, those who reported at least 1 psychotic experience fairly often or very often.

^bThe median age was 29 years.

the positive predictive values (PPVs; probability of the outcome given exposure).

To study the pattern of transition from APS to hospitalization over time, Kaplan-Meier survival graphs were constructed for hospitalization for nonaffective psychotic or other psychiatric disorders as a function of baseline APS.

Finally, we estimated the interaction between social functioning, major depressive disorder, anxiety disorders, alcoholism, cannabis use, and exposure to trauma (factors that may increase the probability of transition from APS to psychotic disorder) on the one hand and the presence of any APS (weak or strong) on the other in the model predicting psychotic hospitalization. The statistical method for assessing interactions was similar to that applied previously⁴⁰⁻⁴³ in that effects were expressed on the additive scale (ie, as a risk difference rather than a risk ratio) using risk difference regression in Stata statistical software, which fits generalized linear models estimating risk differences.^{44,45} The statistical significance of the interactions was assessed by the Wald test.⁴⁶ After calculation of the interaction term, effect sizes of APSs stratified by level of moderator variables were calculated from the model using the appropriate linear combinations with the Stata LINCOM command. A sensitivity analysis modeling interactions on the multiplicative scale was performed as well.

RESULTS

BASELINE DEMOGRAPHIC CHARACTERISTICS AND APSs

The weighted mean (SD) age of the sample in 2007 was 53.7 (2.8) years; 50.2% were male. Of the sample, 57.2% reported at least 1 weak APS and 14.3% reported at least 1 strong APS in the year before the baseline assessment.

At baseline, the mean APS score was higher in younger individuals, subjects of North African origin, cannabis users, those who were single or divorced, and those who

were unemployed (**Table 1**). A significant negative correlation was found between the mean APS score and years of education ($r=-0.16$; $P<.001$), indicating that APSs share some demographic patterns and risk factors with schizophrenia.^{2,47} There was a substantial positive correlation between the mean APS score and the level of non-specific psychological distress ($r=0.56$; $P<.001$), confirming previous work.^{15,27}

PREDICTION OF HOSPITALIZATION FOR NONAFFECTIVE PSYCHOTIC DISORDERS

To assess the effect of APSs on later hospitalization with no assumptions regarding the way in which APSs should be modeled, we examined the association using the mean scores of the PERI false beliefs and perceptions subscale. Higher mean levels of APS scores significantly increased the risk of later hospitalization for nonaffective psychotic disorder (OR=3.60; 95% CI, 1.93-6.70), indicating that with every unit increase in the mean APS score, there was more than a 3-fold increase in the risk of later hospitalization for nonaffective psychotic disorder. This association remained stable when adjusting for age, sex, education, and ethnicity (OR=4.31; 95% CI, 2.21-8.41).

Also, APSs were associated with increased risk for later hospitalization with an ICD-10 diagnosis of narrowly defined schizophrenia (ICD-10 codes F20.0-F20.9) (OR=4.13; 95% CI, 2.21-7.71; adjusted OR=5.35; 95% CI, 2.67-10.70). To increase power, for the remainder of the article we use hospitalization for all nonaffective psychotic disorders as the outcome of interest.

When using the dichotomous yes or no variable for the presence or absence of any APS, the regression model also showed increased association between the presence of any APS in the past year and risk of later hospitalization for a

Table 2. Psychotic Experiences and Association With Later Hospitalization for Nonaffective Psychotic Disorders^a

Exposure	No. (%)		Adjusted OR (95% CI)
	No Hospitalization (n = 4526)	Psychotic Hospitalization (n = 22)	
None	1183 (99.86)	4 (0.14)	1 [Reference]
Weak	2584 (99.49)	11 (0.51)	3.61 (0.78-16.78)
Strong	759 (98.73)	7 (1.27)	9.54 (1.92-47.51)
Adjusted OR linear trend			2.90 (1.49-5.66)

Abbreviation: OR, odd ratio.

^aPercentages are weighted. Nonaffective psychotic disorders had *International Statistical Classification of Diseases, 10th Revision* codes F20.0-F29.9.

nonaffective psychotic disorder (OR=4.64; 95% CI, 1.04-20.70; adjusted OR=4.70; 95% CI, 1.05-21.06).

When examining the linear effects of the number of weak (possible range, 0-13) and strong (possible range, 0-13) APSs, a greater number of weak APSs (OR=1.29; 95% CI, 1.09-1.53; adjusted OR=1.30; 95% CI, 1.10-1.54) or strong APSs (OR=1.35; 95% CI, 1.09-1.67; adjusted OR=1.41; 95% CI, 1.10-1.82) significantly increased the risk of later hospitalization for a nonaffective psychotic disorder. This indicates that with every additional weak or strong APS, there was a 30% or 41% increase, respectively, in the risk of later hospitalization for a psychotic disorder.

Analysis with the 3-level variable representing no APS, any weak APS, or any strong APS revealed a monotonic dose-response association between the strength of the APS and risk of hospitalization for nonaffective psychotic disorder (**Table 2**).

In terms of population attributable risk, 36.0% (weak APS) and 33.0% (strong APS) of the hospitalizations for nonaffective psychotic disorder could be attributed, assuming causality, to the existence of APSs in the population at baseline. The PPV was 0.51% for weak APSs and 1.27% for strong APSs. The PPV was low for all individual APSs in the PERI, although some symptoms displayed higher values, particularly strong APSs of paranoia ("feeling that people wish to harm you"; PPV=4.0%), delusional mood ("feeling that something odd is going on"; PPV=3.5%), and thought withdrawal ("feeling that your thoughts are taken away"; PPV=3.5%).

PREDICTION OF HOSPITALIZATION FOR OTHER PSYCHIATRIC DISORDERS

Higher mean APS ratings significantly increased the risk of later hospitalization for other psychiatric disorders (OR=3.00; 95% CI, 1.57-5.73; adjusted OR=2.21; 95% CI, 1.02-4.82). Examining linear effects of the number of weak and strong APSs on predicting later hospitalization for other psychiatric disorders revealed nonsignificant effects in the same direction. Analysis with the 3-level variable representing no APS, weak APS, or strong APS did not show a significant association between exposure to APS and other psychiatric hospitalizations (**Table 3**).

Table 3. Psychotic Experiences and Association With Later Hospitalization for Nonpsychotic Disorders^a

Exposure	No. (%)		Adjusted OR (95% CI)
	No Hospitalization (n = 4526)	Nonpsychotic Hospitalization (n = 34) ^a	
None	1183 (99.69)	5 (0.31)	1 [Reference]
Weak	2584 (99.40)	18 (0.60)	1.73 (0.58-5.16)
Strong	759 (98.97)	11 (1.03)	2.01 (0.55-7.27)
Adjusted OR linear trend			1.31 (0.71-2.42)

Abbreviation: OR, odd ratio.

^aPercentages are weighted.

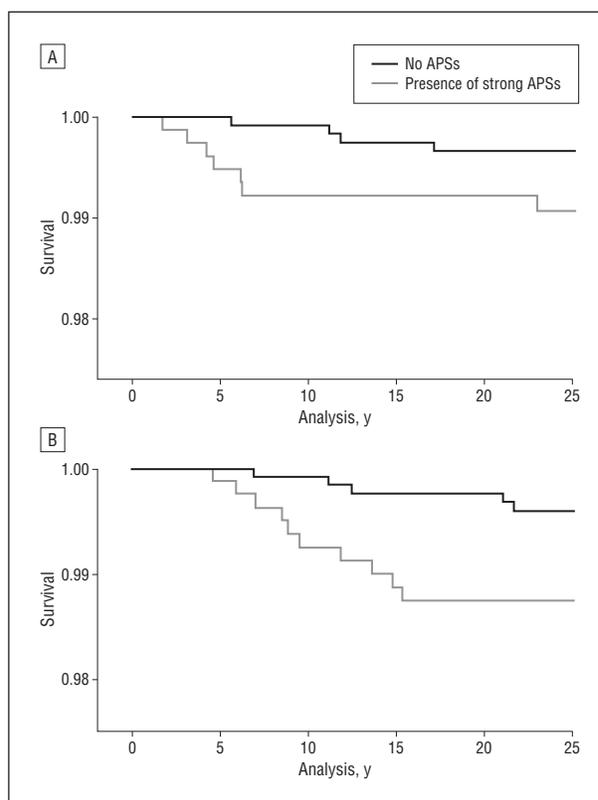


Figure 2. Kaplan-Meier survival curves of strong psychotic experiences and hospitalization for nonaffective psychotic (A) or other, nonpsychotic (B) disorders. APSs indicates attenuated psychotic symptoms.

The Kaplan-Meier survival curves for later hospitalization for nonaffective psychotic disorders showed that the increased risk associated with strong APSs was apparent mostly in the first 5 years after baseline (**Figure 2A**), whereas for other psychiatric disorders the risk incurred by APSs was more spread out during a period of 5 to 15 years (**Figure 2B**).

INTERACTIONS BETWEEN APSs AND OTHER VARIABLES ON RISK OF LATER PSYCHOTIC HOSPITALIZATION

Significant interactions were apparent between poor social functioning ($\chi^2=5.85$; $P=.02$) and anxiety disorders

($\chi^2=9.29$; $P=.002$) at baseline and the presence of any APS in predicting later nonaffective psychotic hospitalizations, suggesting that subjects with APSs and poor social functioning or an anxiety disorder are more prone to hospitalization for nonaffective psychotic disorders. No significant interaction was found between APSs and major depressive disorder, cannabis use, alcoholism, or exposure to trauma, but all interactions were in the hypothesized direction (eTable 2). No interactions were significant on the multiplicative scale, although trends were in a direction similar to that of the findings on the additive scale.

COMMENT

APSs AND LATER SEVERE MENTAL DISORDERS

Among the 4587 subjects sampled from a 10-year birth cohort of young adults and followed up for 24 years, 14.3% of the subjects reported at least 1 strong APS at baseline, but only 0.5% were hospitalized and clinically diagnosed as having a nonaffective psychotic disorder at follow-up. This discrepancy between APSs and clinical diagnoses of nonaffective psychotic disorder is similar to that reported by van Os et al⁴⁸ in the Netherlands Mental Health Survey and Incidence Study (0.4% had nonaffective psychotic disorder; 18% reported APSs) and Kendler et al²⁰ in the National Comorbidity Survey in the United States (0.7% had a clinical diagnosis; 28% reported APSs). Taken together, these findings confirm that in the general population, APSs are much more prevalent than clinically diagnosed psychotic disorders.

A dose-response relationship was observed, with risk for hospitalization increasing with an increasing number of APSs. This is consistent with earlier findings¹³ in which the more APSs there were, the greater the risk was of future psychiatric diagnosis and need for care. This report adds to the existing literature as it is the first to use hospitalization to assess outcome, is based on a birth cohort, and has the longest duration of follow-up. Although some APSs displayed particularly high ORs, the numbers were too small to address the question of whether true differences in predictive value exist as a function of type of APS.

The 95% CIs of weak and strong APSs overlap, suggesting that similar risk is associated with increasing levels of both weak and strong APSs. This may suggest that risk for transition from APSs to psychotic disorder is associated with a threshold effect rather than a linear dose response. Other work, however, is suggestive of a dose-response effect on risk for transition.^{12,13}

Similar to previous reports,^{3,12} the association was significant between APSs and later psychiatric hospitalization but was much weaker for other psychiatric disorders, indicating that APSs might be general predictors of severe mental illness requiring hospitalization that lack both sensitivity and specificity. However, the Kaplan-Meier survival curve showing that almost all of the hospitalizations for nonaffective psychotic disorders in participants with strong APSs occur within 5 years of the baseline assessment (Figure 2A), while hospitalizations for other, nonpsychotic, psychiatric disorders in partici-

pants with strong APSs were spread over 15 years, may indicate some degree of specificity of APSs for nonaffective psychotic disorders.

INTERACTIONS

Given the relatively high attributable risk associated with APSs, it is crucial to learn more about the nature of the association between these nonclinical manifestations and psychotic disorders. One important clue may reside in the finding that the cumulative incidence of later psychotic hospitalization associated with APSs was much higher in respondents with poor social functioning at baseline than in those with normal or high social functioning. This is in line with the centrality of impaired social functioning in schizophrenia⁴⁹ and with evidence emphasizing deficits in social functioning as increasing risk for later schizophrenia,^{24,38,40,50,51} suggesting that a poor outcome of APSs is contingent on the additional presence of poor social functioning.^{52,53} Most of the subsample assessed for social functioning reached predetermined cutoff values on the PERI²⁶ or had a previously diagnosed psychiatric disorder. Unweighted, they would not be representative of the entire cohort. However, as described in "Methods," 416 of the subjects (18.3%) who screened negative in the first stage went through the second stage of assessment in the epidemiological study. We included the weighted social functioning scores and rates of psychiatric diagnoses from these 416 "negatives" in the analyses.

The finding that the presence of anxiety disorders at baseline also significantly interacts with APSs in increasing risk of hospitalization for nonaffective psychotic disorders is in line with reports showing a central role for anxiety in relation to the onset of psychotic symptoms such as paranoia.⁵⁴ The interaction with baseline depression was similarly large, albeit not statistically significant.

There was no indication that the risk of transition to psychotic hospitalization was affected by cannabis use. However, numbers were small and findings were directionally similar to those of social functioning.

The results from the investigations of these interactions should be interpreted with caution, as in all models the variables that made up the interaction (APSs on the one hand and social functioning, cannabis use, major depressive disorder, anxiety disorders, and alcoholism on the other) were significantly associated with each other. In practice, this means that it is difficult to distinguish between moderation (for example, poor social functioning increasing the likelihood of transition from APSs to later psychotic disorder) and mediation (poor social functioning increasing the risk of APSs, which in turn increase the likelihood of transition to psychotic disorder). Nevertheless, both mediation and moderation are important and clinically relevant in this context, and future studies should attempt to distinguish between the two.

IMPLICATIONS ON SCREENING FOR HIGH-RISK STATES

Given the fact that psychotic disorders are usually preceded by sometimes lengthy prodromes, attempts have

been made to identify persons with future disorders when they are in the early stages of a psychosis prodrome.^{55,56} Considerable literature now exists on prodromal clinics that attempt to identify and characterize individuals who will convert to a clinical psychotic disorder in a reasonably short period.^{57,58} These prodromal clinics focus on individuals with attenuated or transitory psychotic symptoms, family history, and decline in functioning,⁵⁹ and recent studies reported 12-month cumulative conversion rates of 10%⁶⁰ and 11%.⁶¹

A major and hitherto unresolved issue regarding the interpretation of these studies is that the base risk of transition from APSs to clinically relevant psychotic disorders in the general population was not known. This study is the first with an unambiguous outcome of psychotic disorder, showing that in the general population, the base risk of transition from APSs to nonaffective psychotic disorder is around 1%, or one-tenth of the estimates in the prodromal literature, during a period of 5 years.

Therefore, the difference between this epidemiological study and the high-risk literature in terms of the PPV (1% vs 10%, respectively) and the time window of conversion (5 years vs 12 months, respectively) can be attributed to the selective sampling strategies used when collecting high-risk, prodromal samples. Our data suggest that the predictors identified by the prodromal clinics might not be relevant to individuals with APSs in the general population. However, it should be noted that the transition rate is likely to depend on the severity and type of APS, which may be skewed by inaccuracies in assessment that may arise from the use of lay-administered questionnaires.

LIMITATIONS

Diagnoses of psychotic disorders in this study were drawn from a hospitalization case registry. This could be of limited value if a large proportion of individuals with psychosis were never hospitalized. However, data from additional ongoing analyses of this Israeli cohort by our group (data not shown) indicate that 93% of the subjects diagnosed as having schizophrenia in the second stage of the study were hospitalized at least once during their lifetime. A related study from England⁶² of never-hospitalized patients with schizophrenia who were receiving outpatient treatment (hence not assessed independently of treatment status as in our epidemiological research) showed that 93.3% of outpatients with schizophrenia were eventually hospitalized at least once in their lifetime.

Although the registry diagnoses are clinical, not research, diagnoses, they are assigned by board-certified psychiatrists who had the benefit of observing the patients throughout 1 or more hospitalizations and had been trained and retrained in the use of the diagnostic criteria of the *ICD-10* and *DSM-IV*. Studies that compared clinical diagnoses of schizophrenia assigned in state hospitals⁶³ with research diagnoses have shown a high degree of concordance, and a previous study by our group comparing registry diagnoses with RDC diagnoses found that the sensitivity of the registry diagnosis of nonaffective psychotic disorders is 0.89, and that of schizophrenia is 0.87.²² In this article, in the interest of increasing power, the main

outcome measure was hospitalization for all nonaffective psychotic disorders (*ICD-10* codes F20.0-F29.9). However, APSs were also significantly associated with increased risk for later hospitalization for narrowly defined schizophrenia (*ICD-10* codes F20.0-F20.9) (adjusted OR=5.35; 95% CI, 2.67-10.70).

We are also limited by lack of data regarding emigrants. However, recent studies on schizophrenia and emigration argue against the possibility that patients more prone to schizophrenia are more likely to emigrate compared with those less prone to schizophrenia.⁶⁴

A potential limitation is the age of the population (mean, 29.4 years), and in fact the mean APS score was slightly higher (approximately 0.2 effect sizes) in younger rather than older participants at baseline (Table 1). Doubtlessly, had we performed the baseline assessment at age 12 years and repeated assessments during years of follow-up, we would have a more complete picture of the relationship between APSs and nonaffective psychotic disorder during the life span, which might be different in adolescents and young adults. That being said, in a meta-analysis of APSs, younger age was not associated with the incidence of APSs and (as in this data set) was only weakly associated with prevalence.^{2,65}

Similarly, one might think that the low transition rate of 0.5% is related to the age of the sample. However, we recently conducted a meta-analysis of transition rates in all available general population epidemiological samples, both young and old, and found similar low rates of transition (around 15 times lower than in high-risk samples).⁶⁶ The limitations notwithstanding, the study has considerable strengths. These include its population-based historical-prospective design, the clinical register follow-up decreasing the danger of false-positive diagnoses generated by lay interviews, minimization of false-negatives caused by nonresponders in interview-based studies, and the ability to exclude all psychotically ill individuals at baseline on the basis of clinical interview.

In summary, self-reported APSs signal risk for later nonaffective psychotic disorder but are not clinically useful as predictors. This relationship between APSs and psychotic disorders is supported by other work showing that APSs are associated with epidemiological risk factors and molecular genetic variation associated with psychotic disorders.⁶⁷ Ultimately, greater understanding of the molecular and cognitive mechanisms of both APSs and psychotic disorders will lead to identification of clinically relevant biological markers predicting which person with an APS will go on to have a psychotic disorder, hence enabling early identification and intervention in psychotic illness.

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