

# Association Between Nonpsychotic Psychiatric Diagnoses in Adolescent Males and Subsequent Onset of Schizophrenia

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**Background:** Nonpsychotic psychiatric symptoms may occasionally herald the later development of schizophrenia. This study followed a population-based cohort of adolescents with nonpsychotic, non-major affective psychiatric disorders to ascertain future hospitalization for schizophrenia.

**Methods:** Results of the medical and mental health assessments on 124 244 16- to 17-year-old males screened by the Israeli draft board were cross-linked with the National Psychiatric Hospitalization case registry, which contains data on all psychiatric hospitalizations in the country, during a 4- to 8-year-long follow-up through age 25 years. In the cohort, 9365 adolescents were assigned a nonpsychotic, non-major affective diagnosis by the draft board.

**Results:** After excluding 167 adolescents who were hospitalized before or up to 1 year after the draft board as-

essment, 1.03% of the adolescents assigned a nonpsychotic, non-major affective psychiatric diagnosis, compared with only 0.23% of the adolescents without any psychiatric diagnosis, were later hospitalized for schizophrenia. Of the patients with schizophrenia, 26.8%, compared with only 7.4% in the general population, had been assigned a nonpsychotic, non-major affective psychiatric diagnosis in adolescence (overall odds ratio [OR], 4.5; 95% confidence interval [CI], 3.6-5.6), ranging from OR, 21.5 (95% CI, 12.6-36.6) for schizophrenia spectrum personality disorders to OR, 3.6 (95% CI, 2.1-6.2) for neurosis.

**Conclusion:** These results reflect the relatively common finding of impaired functioning in patients later hospitalized for schizophrenia and the relatively low power of these disorders in predicting schizophrenia.

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**S**EVERAL prospective longitudinal or follow-up studies suggest that some adolescents who manifest abnormal behavior or personality traits may be at high risk of manifesting mental illness as adults. Adolescents diagnosed as having personality disorders are at increased risk for anxiety, disruptive behavior, affective symptoms, and substance abuse during early adulthood,<sup>1,2</sup> and persons with obsessive-compulsive disorder, social phobia, and panic attacks examined in the National Institute of Mental Health Epidemiologic Catchment Area study<sup>3</sup> were at increased risk for future schizophrenia. The Minnesota Multiphasic Personality Inventory traits of depression, anxiety, internalized anger, social alienation, and withdrawal are associated with increased risk of future schizophrenia.<sup>4</sup> Adolescents with schizotypal personality traits seem to be at a particularly high risk for future psychosis.<sup>5-8</sup> A recent follow-up study of conscripts screened by

the Swedish army found that 18-year-olds with personality disorders, neurosis, substance abuse, or alcohol abuse were at increased risk for future schizophrenia.<sup>9</sup> Similarly, studies of persons with schizophrenia found that some future patients had subnormal intelligence, withdrawn social behavior, conduct and adjustment abnormalities, and very mild neurological deficits<sup>10-15</sup> years before the onset of psychosis. Assessing the prevalence of nonpsychotic psychiatric disorders preceding the diagnosis of schizophrenia is important in understanding the pathophysiologic characteristics of the illness, as some authors<sup>16,17</sup> claim that these abnormalities may reflect a neurodevelopmental origin of illness. In addition, diagnoses with relatively high rates of later hospitalization for schizophrenia might constitute part of a cluster of markers to be used in the future for the early detection of schizophrenia. Such a cluster might include impaired attention,<sup>18</sup> a decrease in the normal inhibition of the P50 auditory-

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## SUBJECTS, MATERIALS, AND METHODS

### SUBJECTS

The study cohort consisted of 124 244 males aged 16 to 17 years who underwent mandatory medical and psychiatric screening by the draft board.

### PSYCHIATRIC ASSESSMENT AT AGE 16 TO 17 YEARS

#### Draft Board Assessment

Israeli law requires that the entire, unselected population of males between the ages of 16 to 17 years undergo a preinduction medical and psychiatric assessment of their eligibility for military service.<sup>25,26</sup> This assessment is performed in regional draft board centers located throughout the country. The screening procedure includes medical and psychiatric history conducted by a physician, and intelligence testing, consisting of 4 multiple-choice subtests testing arithmetic ability, verbal abstraction and concept formation, visuospatial abilities, and the ability to understand written instructions. In addition, an interview assessing personality and behavioral traits is administered by college-aged individuals who participated in a 4-month-long training course on the administration of the interview. Based on the interview and on findings from the physician's examination, adolescents who are suspected of having behavioral disturbances or mental illness are referred for an in-depth assessment by a mental health professional, and if the adolescent warrants a psychiatric diagnosis, he is examined by a board-certified psychiatrist. Criteria for referral to an in-depth mental health assessment include a history of psychological or psychiatric treatment or complaints, manifestation of behavioral abnormalities during the physician's examination or psychometrician's interview, or obtaining the lowest score on the rating of social functioning in the screening interview, which corresponds to the lowest fifth percentile in the population.

The mental health assessment is a comprehensive psychosocial examination performed by a clinical social worker or psychologist who inquires about personal and family history, previous psychological and psychiatric treatments, interpersonal relationships, self-esteem, self-injurious and antisocial acts, and functioning within the family and in school. If the clinician suspects that the adolescent has psychopathologic characteristics, a provisional diagnosis is suggested, and the adolescent is then referred for evaluation to a board-certified psychiatrist experienced in treating adolescents. Adolescents who had previously been treated by mental health professionals, or who had been hospitalized, are required to present treatment summaries and/or discharge letters. Diagnoses during the time covered by this study were based on *International Classification of Diseases, Ninth Revision (ICD-9)* criteria; however, not all ICD-9 diagnoses were used during the period covered by this study. Diagnoses were categorized into 17 major groupings: schizophrenia; schizophreniform disorder; brief reactive psychosis; organic psychotic disorder; major affective disorder, which includes affective disorder with or without psychotic features; avoidant and dependent personality disorders; histrionic personality disorder; obsessive-compulsive personality disorder; narcissistic or borderline or schizoid personality disorders; paranoid personality disorder; antisocial personality disorder; neurosis, which lumps together anxiety, obsessive-compulsive disorder, phobias, chronic posttraumatic stress disorder, and reactive depression; adjustment disorder; combat-related acute stress disorder, equivalent to *DSM-IV* acute stress disorder; alcohol and other drug abuse; and mental retardation. Although schizotypal personality disorder is not an ICD-9 diagnosis, it was also included in the list of draft board diagnoses based on the *DSM-III-R* description, including symptoms of oddity, unusual perceptual experiences, social isolation, and suspiciousness. In cases of comorbidity, the examining psychiatrist decides which diagnosis is most clinically significant, and only that diagnosis is recorded without the comorbid condition. For the sake of simplicity, personality disorders were divided into 3 groups: (1) schizophrenia spectrum personality disorders (schizotypal and

evoked response to the second of paired stimuli,<sup>19</sup> and impaired eye tracking.<sup>20</sup>

The current study combined data from the mental health screening assessment performed by the Israeli draft board, with data from the Israel Psychiatric Hospitalization Registry. The study is unique in that it is based on data from the complete, nationwide population of male adolescents, and it contains information on absolutely all psychiatric hospitalizations in the country. To evaluate the association between manifestation of nonpsychotic, non-major affective psychiatric disorders in adolescence and later manifestation of schizophrenia, (1) adolescents with nonpsychotic, non-major affective psychiatric disorders in adolescence were followed up to ascertain the risk of hospitalization for future schizophrenia, and (2) the prevalence of nonpsychotic, non-major affective psychiatric disorders during adolescence was ascertained in persons diagnosed with schizophrenia. It was hypothesized that nonpsychotic, non-major affective psychiatric diagnoses, particularly

schizophrenia-spectrum personality disorders (SSPDs) (ie, paranoid or schizotypal personality disorders), would be more prevalent among future schizophrenic patients compared with persons not later hospitalized for schizophrenia.

Because subnormal intellectual functioning is present in some persons with nonpsychotic psychiatric disorders<sup>21-24</sup> and is also a risk factor for schizophrenia,<sup>10</sup> the influence of intellectual functioning as a confounding factor for the risk for schizophrenia in adolescents with nonpsychotic, non-major affective psychiatric disorders was also assessed.

## RESULTS

The follow-up of adolescents with nonpsychotic, non-major affective psychiatric diagnoses found that having any nonpsychotic, non-major affective psychiatric disorder in adolescence increased the risk of future hospitalization for schizophrenia compared with the risk for

paranoid personality disorders), (2) antisocial personality disorder, and (3) other personality disorders (avoidant, dependent, histrionic, obsessive-compulsive, narcissistic, borderline, or schizoid personality disorders). Because this article focuses on the risk for future schizophrenia in adolescents with nonpsychotic, non-major affective psychiatric diagnoses, adolescents diagnosed with affective disorders by the draft board were not included in the analysis, as some of the adolescents with affective disorders had psychotic as well as affective symptoms. Of the 124 244 male adolescents screened, 9365 were diagnosed with a nonpsychotic, non-major affective psychiatric disorder.

### Hospitalizations for Schizophrenia

The National Psychiatric Hospitalization Case Registry is a complete listing of all psychiatric hospitalizations in the country, including the diagnosis assigned and coded on admission and discharge by a board-certified psychiatrist at the facility. During the time covered by this study, ICD-9 diagnoses were used by the registry. All inpatient psychiatric facilities in the country, including psychiatric hospitals, day hospitals, and psychiatric units in general hospitals, are required by law to report all admissions and discharges to the registry.

The National Psychiatric Hospitalization Case Registry was used to identify those adolescents screened by the draft board who were later hospitalized for schizophrenia. From the complete cohort of 124 244 adolescents, during a follow-up of 4 to 8 years (oldest person at time of follow-up was aged 25 years), a total of 577 males were hospitalized with a diagnosis of schizophrenia, bringing the risk for schizophrenia in this population to 0.46%, which is comparable to the age-adjusted incidence of schizophrenia in other studies carried out in Israel<sup>27</sup> and the United States.<sup>28,29</sup>

The current analysis focused on those adolescents diagnosed by the draft board with a nonpsychotic, non-major affective psychiatric disorder who were later hospitalized for schizophrenia. To underscore the distinction between the diagnosis of a nonpsychotic psychiatric disorder and the hospitalization associated with a diagnosis

of schizophrenia, all adolescents (n=167) who were hospitalized for schizophrenia prior to or within 1 year after the draft board assessment were excluded from the analysis. Using these criteria, of 9365 adolescents diagnosed with a nonpsychotic, non-major affective psychiatric disorder by the draft board, 96 (1.03%) were later hospitalized for schizophrenia. In comparison, 0.23% of the population of adolescents who did not have a psychiatric diagnosis by the draft board were later hospitalized for schizophrenia.

### STATISTICAL ANALYSIS

The main analyses used odds ratios (ORs) that, in view of the relative rarity of the outcome (hospitalization for schizophrenia), estimated the desired incidence rate ratio. The ORs and 95% confidence intervals (CIs) were calculated using SAS computer software (SAS version 6.12; SAS Institute, Cary, NC).

Subnormal intellectual functioning is present in some persons with nonpsychotic psychiatric disorders<sup>21-24</sup> and is also associated with future schizophrenia in this population of adolescents (OR, 2.16; 95% CI, 2.004-3.430) and in other similar populations.<sup>12</sup> We therefore asked if subnormal intellectual performance is a confounding factor for the risk for schizophrenia in adolescents with nonpsychotic psychiatric disorders. The association between each psychiatric diagnosis and later hospitalization for schizophrenia was recalculated while controlling for intellectual performance. In this analysis we applied separate hierarchical logistic regression models for each of the psychiatric diagnoses. In each regression model, intellectual performance was entered first, and the psychiatric diagnosis was entered in the second step.

The risk of hospitalization for schizophrenia for adolescents with different nonpsychotic psychiatric diagnosis was also a function of the follow-up period; the longer the follow-up period, the greater the chances of hospitalization for schizophrenia. To ascertain differences in follow-up periods for different diagnoses, the mean follow-up time for adolescents with each draft board diagnosis, or with no draft board diagnosis, were compared using analyses of variance.

schizophrenia in the entire cohort of adolescents. The **Table** displays the number of adolescents who were assigned nonpsychotic, non-major affective psychiatric diagnoses by draft board psychiatrists and the rate of later hospitalization for schizophrenia. The prevalence of nonpsychotic, non-major affective psychiatric disorders in future schizophrenia patients was 26.8% compared with 7.4% of nonpsychotic, non-major affective psychiatric disorders in the general population of adolescents (OR, 4.5; 95% CI, 3.6-5.6).

An association was found between the different disorders in adolescence and schizophrenia. The magnitude of this association differed between the different diagnostic groups. For example, patients with a registry diagnosis of schizophrenia were approximately 21.5 times more likely to have had a premorbid diagnosis of SSPD in adolescence compared with the prevalence of SSPD in the general population of adolescents. On the other hand, patients with a registry diagnosis of schizophrenia were only about 3.6 times more likely to have had a

premorbid diagnosis of neurosis in adolescence compared with the prevalence of neurosis in the general population of adolescents.

The mean follow-up period for adolescents with each nonpsychotic psychiatric diagnosis, or with no draft board psychiatric diagnosis, was significantly different, the mean follow-up periods ranging from 7.0 to 7.4 years (SD, 1 year) ( $F_{7,124234}=36.15, P<.001$ ). Controlling for intellectual functioning decreased the association with future schizophrenia for most of the nonpsychotic disorders, with the decreases in OR reaching 65% across the different diagnoses (Table).

### COMMENT

In this population-based cohort, approximately 26.8% of the males hospitalized for schizophrenia had nonpsychotic, non-major affective psychiatric disorders in adolescence compared with a prevalence of 7.4% of nonpsychotic, non-major affective psychiatric disorders in the

**Association Between Nonpsychotic Psychiatric Diagnoses and Later Hospitalization for Schizophrenia in a Population of 17-Year-Old Males**

Diagnosis	Prevalence in Total Population, % (N = 124 244)*	Prevalence in Future Schizophrenia Patients, % (n = 358)†	Hospitalized for Schizophrenia, No. (%)‡	Approximate OR (95% CI)§	Approximate OR Controlled for IQ (95% CI)
Schizophrenia-spectrum personality disorders	0.11	1.95	7/149 (4.7)	21.5 (12.6-36.6)	14.4 (5.9-29.4)
Adjustment disorder	0.03	0.28	1/38 (2.6)	11.8 (2.5-55.2)	12.2 (0.7-58.7)
Antisocial personality disorder and impulse control disorder	0.15	1.11	4/200 (2.0)	8.9 (3.9-20.3)	4.8 (1.4-11.4)
Mental retardation	0.49	2.79	10/628 (1.6)	7.1 (4.1-12.1)	3.2 (1.5-6.1)
Alcohol and drug abuse	0.05	0.27	1/64 (1.5)	6.8 (1.2-37.4)	5.3 (0.3-24.9)
Other personality disorders¶	5.43	17.03	61/6816 (0.9)	3.9 (3.0-5.1)	2.7 (2.0-3.6)
Neurosis#	1.17	3.35	12/1470 (0.8)	3.6 (2.1-6.2)	2.5 (1.3-4.4)
Total nonpsychotic diagnoses	7.43	<b>26.82</b>			

\*Entire population, including adolescents hospitalized within a year of draft board assessment and adolescents diagnosed with psychotic or affective disorders during draft board assessment.

†Does not include 167 adolescents hospitalized prior to or within 1 year of draft board assessment, or 52 adolescents diagnosed with psychotic or affective disorders during draft board assessment.

‡Number of adolescents later diagnosed for schizophrenia/number of adolescents assigned nonpsychotic psychiatric diagnosis.

§OR indicates odds ratios; CI, confidence interval.

||Paranoid personality disorder or schizotypal personality disorder.

¶Obsessive-compulsive personality disorder (OCD), avoidant personality disorder, dependent personality disorder, narcissistic personality disorder, schizoid personality disorder, borderline personality disorder, or histrionic personality disorder.

#Anxiety, phobias, OCD, reactive depression, or posttraumatic stress disorder.

general population of adolescents. These findings are consistent with and expand on previous studies<sup>10-15</sup> that found that persons with schizophrenia often have behavioral and emotional disturbances years before the manifestation of psychosis. More unique are the findings of the follow-up, which found that adolescents with nonpsychotic, non-major affective psychiatric disorders had an increased risk for future schizophrenia (1.03%) compared with the risk for schizophrenia in the entire population (0.46%). Taken together, these may indicate that although many patients with schizophrenia have behavioral deviations in adolescence, these behavioral deviations alone, without exploring subjective experience,<sup>30,31</sup> lack the specificity necessary to predict future schizophrenia.<sup>30,31</sup> This is because most adolescents (approximately 99%) who have nonpsychotic, non-major affective psychiatric disorders do not later have schizophrenia.

Another singular finding of this report is the gradient of association between the various psychiatric disorders and future schizophrenia. While the ORs of persons with other personality disorders and neuroses were 3.6 to 3.9, adolescents with antisocial personality disorder, mental retardation, or drug abuse had ORs in the range of 7 to 9. Moreover, adolescents with SSPDs had an OR of 21.5. It could be hypothesized that those nonpsychotic, non-major affective psychiatric disorders with higher ORs share more genetic or environmental factors in common with schizophrenia. This makes sense particularly for the SSPDs, which are phenomenologically more similar to schizophrenia.<sup>32</sup>

The data presented here are consistent with high-risk studies<sup>33-43</sup> of children and siblings of persons with schizophrenia that found increased prevalence of nonpsychotic symptoms and diagnoses in these persons and increased prevalence of schizophrenia at follow-up. Furthermore, the finding that adolescents with SSPDs have

increased chances of future schizophrenia replicates and expands other studies, which found that magical thinking<sup>6,7</sup> and schizotypal symptoms<sup>5</sup> increase the risk of future schizophrenia. Drug abuse also has been reported by others to be a risk factor for future schizophrenia<sup>44,45</sup>; our finding of alcohol and other drug abuse as significant risk factors (OR, 6.8) is consistent with these findings. The findings in this report replicate very closely a recently published article with a similar design,<sup>9</sup> which followed conscripts screened by the Swedish draft board for future hospitalization for schizophrenia. That study reports that 38% of the future patients had a diagnosis of nonpsychotic psychiatric disorder at age 18 years, with ORs of 4.6 for neurosis, 8.2 for personality disorder, 5.5 for alcohol abuse, and 14.0 for substance abuse. The great similarity of the findings in that article with the present report supports the reliability of the data reported here.

Subnormal intellectual functioning is present in some persons with nonpsychotic psychiatric disorders<sup>21-24</sup> and is also associated with future schizophrenia in this and other populations<sup>12</sup> of adolescents (OR, 2.16; 95% CI, 2.004-3.430). We therefore controlled for the effect of intellectual performance on the risk for schizophrenia. We found that when intellectual functioning is controlled for, the association of nonpsychotic, non-major affective psychiatric diagnoses with future schizophrenia is decreased by up to 65% across the different diagnoses. This suggests that although subnormal intelligence confounds the risk of later hospitalization, having a nonpsychotic, non-major affective psychiatric diagnosis in adolescence still increases the risk for future schizophrenia independent of subnormal intelligence.

The follow-up period covered by this study, between 4 to 8 years, is not long enough to include all cases of future schizophrenia in this cohort; a longer follow-up period would enable identification of additional cases. There were slight differences in mean follow-up

time between adolescents with different diagnoses, which might have affected the ORs. However, these differences were slight, up to 4 months, and are not likely to significantly affect these results.

The diagnoses assigned by draft board psychiatrists are not research but clinical diagnoses, raising concerns about their accuracy. However, all the psychiatrists working for the draft board are board certified, received their postgraduate education after the introduction of *DSM-III*, and are instructed and supervised on a regular basis for quality and consistency. The 3-stage screening procedure used by the draft board dictates that before the adolescent is referred to the psychiatrist, the interviewer assessing personality and behavioral traits and the clinical social worker or clinical psychologist must identify him as having significant behavioral problems. In addition, the clinical social worker or clinical psychologist assigns a tentative diagnosis, so that the psychiatric diagnosis assigned reflects the consensus diagnosis. Disagreements between the two are resolved by consensus with the help of another senior psychiatrist. This being said, because the reliability of the *ICD-9* is known to be problematic,<sup>46,47</sup> the comparison of risks between different diagnostic categories must be regarded as tentative.

The prevalence of nonpsychotic, non-major affective psychiatric diagnoses made by the draft board in the population of adolescents, approximately 7.4%, is lower than the prevalence of psychiatric disorders found in some, but not all, other studies; a review<sup>48</sup> of the prevalence of psychiatric diagnoses in children and adolescents living in the community found a mean prevalence of 15% (range, 1%-51%). One reason for the relatively low prevalence rates observed may be that the draft board screening procedure sets a high threshold for diagnosis of minor psychiatric disturbances compared with screening instruments used in epidemiological surveys. For example, diagnoses such as specific phobias (included here in the "anxiety" category) that are relatively common in epidemiological surveys are less common in the present sample. The prevalence of substance abuse in the population is also low. This has been reported in a previous study on the epidemiology<sup>27</sup> of psychiatric disorders in young adults in Israel, which also found low prevalence of substance abuse compared with the prevalence of substance abuse in the United States or Europe. In addition, the differences in prevalence may be partially explained by the fact that this cohort included only males, whereas females have, in some but not all studies, a higher rate of psychiatric disorders.<sup>49-51</sup> However, even if some individuals who merited a diagnosis of nonpsychotic and non-major affective psychiatric disorders were overlooked, this does not invalidate the associations reported here.

A related concern is the fact that the case registry diagnoses are clinical, not research diagnoses. However, these diagnoses too are assigned by board-certified psychiatrists who have had the benefit of observing the patient throughout one or more hospitalizations, and have been trained and retrained in the use of the diagnostic criteria of the *ICD-9*. Moreover, studies that have compared clinical diagnoses of schizophrenia assigned in state

hospitals<sup>52</sup> with research diagnoses have shown a high degree of concordance. It is clear that the optimal design of a study assessing the association between nonpsychotic psychiatric disorders in adolescence and future schizophrenia would screen subjects using structured instruments to ascertain diagnoses both of the nonpsychotic psychiatric disorders and of schizophrenia. However, the incidence of schizophrenia in the population is between 0.5% and 1%, and not all patients have abnormal personality functioning before manifesting psychosis. To yield significant results, this hypothetical protocol would therefore necessitate screening of hundreds of thousands of adolescents and then following them for years, a project that is probably not feasible in the near future.

In summary, the results of this study, based on the screening of an entire population of 16- to 17-year-old males, indicate that nonpsychotic, non-major affective psychiatric disorders in adolescence are associated with future schizophrenia. The predictive power of SSPDs in particular, although significant, is not strong enough to recommend prophylactic treatment with antipsychotic or other medications. Hence, these data advocate for intensive research in this area rather than suggesting immediate clinical implications. Additional studies combining information about genetic, obstetric, and intellectual risk factors, together with behavioral disturbances in adolescence, may enable more accurate identification of persons who will later have schizophrenia.

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