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Testing the Psychosis Continuum: Differential Impact of Genetic and Nongenetic Risk Factors and Comorbid Psychopathology Across the Entire Spectrum of Psychosis

Tolga Binbay[1,2], Marjan Drukker[2], Hayriye Elbi[3], Feride Aksu Tanık[4], Ferda Özkınay[5], Hüseyin Onay[5], Nesli Zağlı[6], Jim van Os[*,2,7], and Köksal Alptekin[8]

[1]Department of Psychiatry, Atatürk State Hospital, Sinop, Turkey; [2]Maastricht University Medical Centre, School of Mental Health and Neuroscience, Department of Psychiatry and Psychology, South Limburg Mental Health Research and Teaching Network, PO Box 616, Vijverdal, 6200 MD Maastricht, The Netherlands; [3]Department of Psychiatry, School of Medicine, Ege University, Izmir, Turkey; [4]Department of Public Health, School of Medicine, Ege University, Izmir, Turkey; [5]Department of Medical Genetics, School of Medicine, Ege University, Izmir, Turkey; [6]Department of Neuroscience, Institute of Health Sciences, Dokuz Eylül University, Izmir, Turkey; [7]Department of Psychosis Studies, Institute of Psychiatry, King's Health Partners, King's College, De Crespigny Park, Denmark Hill, London, UK; [8]Department of Psychiatry, School of Medicine, Dokuz Eylül University, Izmir, Turkey

*To whom correspondence should be addressed; tel: +31 43-3875443, fax: +31 43-3875444, e-mail: j.vanos@MaastrichtUniversity.nl

A growing number of studies demonstrate high rates of subthreshold psychotic experiences, but there is considerable heterogeneity in rates due to study cohort and design factors, obscuring how prevalent psychotic experiences may or may not relate to rare psychotic disorders. In a representative general population sample (n = 4011) in Izmir, Turkey, the full spectrum of expression of psychosis was categorized across 5 groups representing (1) absence of psychosis, (2) subclinical psychotic experiences, (3) low-impact psychotic symptoms, (4) high-impact psychotic symptoms, and (5) full-blown clinical psychotic disorder and analyzed for continuity and discontinuity in relation to (1) other symptom dimensions associated with psychotic disorder and (2) proxies of genetic and nongenetic etiology. Results were tested for linear and extralinear contrasts between clinical and nonclinical and between disorder and nondisorder expression of psychosis. Demographic variables, indexing premorbid social adjustment and socioeconomic status, impacted mostly linearly; proxy variables of genetic loading (more or more severely affected relatives) impacted in a positive extralinear fashion; environmental risk factors sometimes impacted linearly (urbanicity and childhood adversity) and sometimes extralinearly (cannabis), occasioning a disproportional shift in risk at the clinical disorder end of the spectrum. Affective symptoms were associated with a disproportionally higher risk below the disorder threshold, whereas a disproportionally higher risk above the threshold was associated with psychotic symptom load, negative symptoms, disorganization, and visible signs of mental illness. Liability associated with respectively affective and nonaffective symptom domains, in interaction with environmental risks, may operate by impacting differentially over a quasi-continuous extended psychosis phenotype in the population.

Key words: psychosis continuum/schizophrenia/epidemiology

Introduction

A large and growing number of studies have examined subthreshold expressions of the positive symptoms of psychosis in the general population and established that there is a degree of demographic (sharing the same age-related expression), etiological (sharing family history of psychotic disorder and environmental risk factors, such as cannabis, minority group position, childhood adversity, and urbanicity), psychopathological (associations with negative symptoms and cognitive alterations), and, arguably most importantly, longitudinal continuity predictive of clinical outcome (reviews by[1–3]).

However, despite the large number of studies, research on psychotic experiences in the general population remains in its early stages, given that a recent meta-analysis showed that half of the heterogeneity in rates of subclinical psychotic experiences across studies is due to study cohort and design factors.[3] Furthermore, systematic review of the literature shows that there is evidence not only for a psychometric "continuum" (in the sense of an extended psychosis phenotype blending gradually into clinical syndromes)[1] but also for an underlying latent categorical structure of the population (in the sense that regardless of the presence

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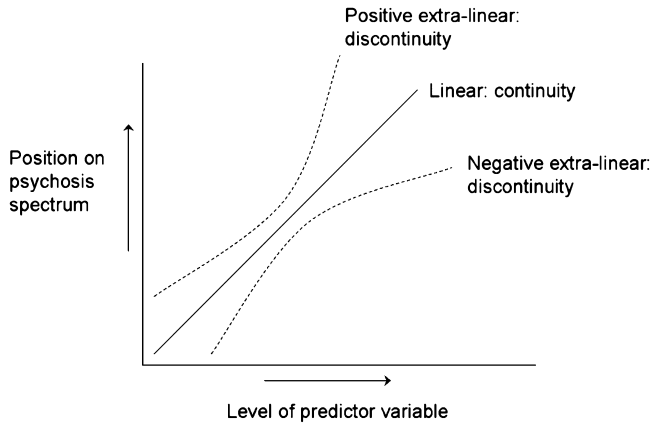


Fig. 1. Continuity and discontinuity underlying apparent continuum. Progression from subthreshold psychotic states to clinical psychotic outcome (Y-axis) may be influenced by a range of predictor variables (X-axis). The association between a particular predictor variable and position on the psychosis spectrum may be increasing linearly with increasing level of the predictor variable (continuity) or alternatively there may be a disproportional shift (up or down the psychosis spectrum) across the continuum beyond a certain level of the predictor variable, giving rise to qualitative differences at the end of an observed quasi-continuum.

of a psychometric continuum, the population may still be composed of 2 different types of people).[3]

Therefore, several issues relating to the "extended psychosis phenotype[4]" are in urgent need of further inquiry:

1. Although studies have attempted to capture the expression of psychosis outside psychotic disorder, no study to date has attempted to describe, in an epidemiological sample, the full spectrum of severity ranging from "psychotic experiences," without dysfunction or impairment, to "psychotic symptoms," with variable degree of dysfunction and impairment but below the threshold of formal diagnosis, to "psychotic disorder."
2. Studies to date have almost exclusively focused on positive psychotic experiences, without modeling relationships with other symptom dimensions seen in psychotic disorder, notably affective symptoms and negative symptoms.
3. There have been only few attempts[5,6] to clarify what is actually meant by (expressed or implied) continuity.[7] The fact that subthreshold psychotic states predict clinical outcomes may be caused by underlying extralinear associations occasioned by unmeasured moderators, giving rise to qualitative differences at the end of an observed quasi-continuum[8] (see figure 1). Suggestive findings in this regard come from a handful of prospective general population studies showing that the onset of psychotic disorder can be seen as the outcome of earlier subthreshold expressions of psychotic signs and symptoms but that transition crucially codepends on other factors, such as number, severity, and degree of persistence of subthreshold psychotic symptoms; the specific combination of delusions and hallucinations (representing a crucial deepening of the psychotic process[9]); a context of affective dysregulation and negative symptoms; and exposure to environmental risk factors, such as childhood adverse life events, cannabis use, and an urban environment.[9–15] It is not known that to what degree these influences bring about a graded increase in risk (continuity) or whether they occasion threshold effects in the form of a sudden increase in risk beyond a certain value (discontinuity).

In the current study, therefore, an attempt was made to capture, in an epidemiological sample, the full range of expression of psychosis and order them according to severity and impact, so as to be able to describe the full spectrum. This allowed us to test directly to what degree associations between the different levels of the psychosis spectrum on the one hand and etiological, psychopathological, and demographic variables on the other were characterized by either graded linear or more discontinuous extralinear relationships. All deviation from linearity was tested on the same additive scale for both continuous and binary variables.

Methods

The TürkSch study consisted of a 3-stage data collection to assess individual, family, and neighborhood level variables.[16] The study aimed to assess the prevalence of mental health problems with a special focus on psychotic outcomes (stage 1) and social capital in wards in the city of Izmir, Turkey (stage 2). The last stage (stage 3) was a nested case-control study that recruited individuals with psychotic outcomes and healthy controls from stage 1.[16] The present article uses data collected in stage 1. The TürkSch study has been described in more detail in a previous article.[16]

Sample

The study was approved by the Ege University ethics committee, and subjects provided written informed consent. Six thousand households were randomly selected from the Izmir population using a multistage sampling procedure.[17] First, the Turkish Institute of Statistics (TURKSTAT) selected 6000 households stratified by 4 categories of urbanicity including rural areas in the wider Izmir area and provided the addresses to the investigators. The Ege University team sent letters to each selected address to announce a visit and interviewers visited each address. After providing informed consent, 1 household member aged between 15 and 64 years and available to complete the interview was randomly selected using the Kish within-household sampling method.[18] If one of the residents of the household was already diagnosed with a psychotic disorder, he or she was recruited for the study

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without application of the Kish method. Persons who were not immediately available (due to hospitalization, military service, travel, imprisonment, or acute exacerbation of a mental disorder) were contacted later in the year. The sample thus covered 294 of the 348 administrative urban wards in Izmir with an additional 8 rural wards located at least 30 km from the city center.

Interviewers, Interviewer Training, and Quality Control

Lay interviewers had at least high school education, a health-related profession, and/or were experienced in doing field surveys.[16] Training of the interviewers included basic information on mental health problems, symptom dimensions in psychosis, fieldwork, and ethical as well as medicolegal aspects. Training for the Composite International Diagnostic Interview (CIDI) was carried out using official CIDI training material. Bimonthly briefing meetings were arranged to exchange and share experiences and prevent interviewer "drift." In order to monitor and conduct quality checks of the visits and interviews over the entire data collection period, each interview was assessed using a standard procedure for formal consistency, appropriate recording and coding.[16]

An attempt was made to reduce the number of missing values on any section of the questionnaire by making, if necessary, a phone call to the respondent and obtain missing information. When the quality of the interview was deemed low or if too many data were missing, a second visit was planned by a different interviewer. Thus, a total of 392 reinterviews were carried out in order to ensure data quality and completeness.

Screening and Diagnostic Instrument

In order to assess psychotic experiences and to diagnose disorders with psychotic features, assessments were based on the relevant sections of the CIDI 2.1.[19] The CIDI is a fully structured interview developed by the World Health Organization[20] and has been used in various surveys around the world including Turkey.[21–24] Primarily designed for use in epidemiological studies of mental disorders, the CIDI can be used by both clinicians and trained interviewers. CIDI-based screening of symptoms provides diagnoses of various mental disorders in accordance with the definitions and criteria of the *International Classification of Diseases, Tenth Revision* (ICD-10),[25] and *Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition)* (DSM-IV),[26] along with information about frequency, duration, help-seeking, severity of symptoms, and psychosocial impairment. In the current study, assessment included screening sections on tobacco, alcohol and substance-related disorders, depressive and dysthymic disorders, manic and bipolar affective disorders, schizophrenia and other psychotic disorders, posttraumatic stress disorder, and 2 final sections containing concluding questions, interviewer observations, and interviewer ratings. The time frame of the CIDI was lifetime for the G-section of psychotic symptoms and the past year for all other items.

Rating of psychotic symptoms can be difficult because sometimes individuals can be describing a plausible event that in the CIDI may be rated as a psychotic symptom. Therefore, the following procedures were followed. First, during the interview, each time a participant endorsed a CIDI psychotic symptom, the participant was asked to give an example, which was written down verbatim by the interviewer for later review with the mental health clinician on the team. All CIDI interviews were reviewed by the clinician (psychiatrist and/or psychologist with at least 5 y clinical experience) and if it was not clear whether or not the participant had truly endorsed a psychotic symptom, they were recontacted by the clinician over the telephone for CIDI reinterview ($n = 128$) or, if that was not possible, for an interview at their residence ($n = 49$).

All participants, and the family, were asked if the person had ever been treated for a mental health problem and/or had received a diagnosis of psychiatric disorder. If this was the case, the person was asked for permission to contact the clinician involved in the diagnosis or the treatment of the participant in order to verify the diagnosis and review case material.

In order to identify individuals with psychotic disorder, several layers and steps of case identification were applied. All individuals endorsing at least 1 CIDI psychotic symptom associated with help-seeking or, if there was no help-seeking, occurring with a frequency of at least once a week were recontacted by the study team and invited for a clinical evaluation with the Structured Clinical Interview for DSM-IV (SCID)[27] by the team psychiatrist and psychologist. Individuals (225 of 296) were thus successfully recontacted and reinterviewed.

Dependent Variable

The main analytical outcome was a categorical variable, in which severity of symptoms and impairment associated with symptoms were combined. The measure of impairment was based on 7 binary CIDI items indexing help-seeking for delusions (G16), help-seeking for hallucinatory experiences (G23), interference with functioning (G28), duration of symptoms (G25; at least 1 wk), frequency of symptoms (G26; at least "sometimes"), being unable to enjoy relationships (G29a), and being unable to work due to symptoms (G29). The 7 variables were all moderately to strongly correlated with each other (Pearson's correlation coefficient .5–.8) and principal component analysis revealed a single component with eigenvalue greater than unity (4.7) explaining 67% of the variance. The variables were therefore combined into a single scale,[15] consisting of the sum score of the items, with good internal consistency (Crohnbach's alpha: .91).

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Using this information, a sum score impairment was constructed with a minimum of 0 and a maximum of 7.

Guided by previous literature,[12,13,28] a psychosis "spectrum" variable was constructed, including 5 categories. Psychotic disorder (category 4, $n = 99$) included all individuals with (1) a past or current DSM-IV diagnosis of any disorder with psychotic symptoms, based on hospital diagnosis, any health care-based diagnosis, or other clinical register diagnosis or (2) diagnosis at clinical reinterview with the SCID. Categories 1–3 all included individuals who scored positive on the psychosis screening questions but did not have psychotic disorder. In the subclinical psychotic experience group (category 1, $n = 625$) impairment score was zero. Low-impact psychotic symptoms (category 2, $n = 198$) included individuals with impairment scores between 1 and 3 and high-impact psychotic symptoms (category 3, $n = 109$) individuals with impairment scores between 4 and 7. All other individuals were included in the reference category (0, absence of psychosis, $n = 2980$).

Psychotic Symptoms

Psychotic symptoms were rated using 14 CIDI delusions items (G1, G2, G3, G4, G5, G7, G8, G9, G10, G11, G12, G13, G13b, and G14) and 5 CIDI hallucinations items (G17, G18, G20, G20C, and G21). All items were rated dichotomously indicating presence or absence. Three sum scores were generated representing the number of psychotic symptoms, the number of delusions, and the number of hallucinations. In addition, guided by previous literature,[9] a dichotomous variable reflecting the combination of at least 1 delusion and at least 1 hallucination (delusions and hallucinations) was constructed. In addition, the interviewers rated a variable reflecting their clinical impression: Whether or not they thought the subject was mentally ill.

Nonpsychotic Symptoms

Guided by previous research,[14,29] 2 affective symptoms sum scores were generated. Depressive symptoms (range 0–10) included the 10 symptoms (DSM-IV and ICD-10) of the CIDI depression section (depressed mood, loss of interest, lacking energy, appetite change, sleep problems, being slow or restless, feelings of worthlessness or guilt, decreased self-esteem, trouble thinking or indecisiveness, and thoughts of death). Depressive symptoms were only rated if any of the core items (depressed mood and loss of interest) were endorsed as having been present for 2 weeks. Mania (manic and hypomanic symptoms; range 0–12) included 12 symptom items of the CIDI mania section (elevated mood, irritability, goal-directed activity, psychomotor agitation, spending sprees, sexual indiscretions, increased talkativeness, flight of ideas, loss of normal social inhibitions, increased self-esteem or grandiosity, decreased need for sleep, and distractibility). Hypomanic and manic symptoms were assessed only if any of the core items (elevated mood and irritability) had been present during 4 successive days. Only participants having core hypomanic and mania symptoms that were either noticed by others or because of which participants had experienced problems were included.

The negative symptoms sum score was assessed using 4 symptom items of the CIDI P section, a section on interviewer observations (flat affect, slow speech, poverty of speech, and impaired ability to initiate activity). Because the prevalence was low, this sum score was recoded into a dichotomous variable (0 = 0 and other = 1). The disorganization sum score was also assessed using the CIDI P section (neologism, thought disorder, and hallucinatory behavior) and was dichotomized into absence (0) vs at least 1 symptom (1).

Other Assessments

The interview included a sociodemographic questionnaire in order to determine various risk factors and background characteristics. Ethnicity (Turkish, Kurdish, Balkan Turks, Arabic, and Others) was recoded into Turkish and non-Turkish. Marital status (single, divorced, married, and widowed) was recoded into ever married and never married. Socioeconomic status was based on profession and recoded into 4 ordinal categories (1: I and II professional and IIIA nonmanual high employees, 2: IIIB nonmanual low employee and V and VI skilled workers and technicians, 3: IVA, IVB, and IVC owners of small businesses, and 4: VIIA and B manual workers).[30] Drop in socioeconomic status was the difference between parental and current socioeconomic status of the subject when socioeconomic status was lower in the subject.

Using questions derived from the Family Interview for Genetic Studies[31] on mental health problems in the father, mother, siblings, and offspring, the number of family members with such problems was calculated. This resulted in 2 variables indicating "1 family member" and "2 or more family members with mental health problems," respectively. In addition, the type of mental health problems in the family was assessed and recoded into a variable indicating common mental disorder (depression and anxiety), but no severe mental illness (SMI) in the family and a variable SMI in the family (with or without common mental disorder).

Childhood adverse life events between age 0 and 5 years and between age 6 and 15 years were included in the interview. Adverse life events were death of any parent, divorce of parents, and separation from parents for at least for 3 months. A dichotomous variable was constructed reflecting presence of any adverse life events between 0 and 15 (yes/no).

Similarly, urbanicity of the birthplace and of the place where children lived between the age of 6 and 15 years was determined using population density measures in

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the 1990 census (TURKSTAT). Urbanicity at birth and urbanicity at age 6–15 years were included in the analyses as 2 separate variables (4 categories: village or district population <50 000; 50 000–200 000; province >200 000; district in metropolitan area; these 4 categories were recoded into 2, with cut-off point 200 000, for the calculation of ORs). Cannabis use was also included in the CIDI. Conform previous CIDI-based research,[32] lifetime cannabis use of 5 times or more was defined as exposure status for cannabis.

Response

Of 6000 addresses, 5242 households were eligible for interview. Main reasons for ineligibility were change of address, incorrect address, and addresses with residents not meeting the inclusion criteria (not aged between 15 and 65 y). In the 5242 eligible households, a total of 4011 individuals were successfully interviewed, resulting in a response rate of 76.5%. Main reasons for nonresponse were refusal to participate (18.2%), failure to contact anyone in the identified household (3.1%), and failure to contact the sampled individual in an identified household (3.0%). More details have been described elsewhere.[16]

Statistical Analyses

All analyses were performed using STATA (version 11[33]) and a priori adjusted for age and sex. The main analytical outcome of the study was the 5-level spectrum variable, coded 0–4 as described earlier.

Associations between spectrum and other variables were expressed as regression coefficients, derived from linear regression (continuous variables, *B*) or logistic regression (dichotomous variables, OR) of these variables with the variable spectrum as independent variable recoded into dummies, absence of psychotic experiences being the reference category. Spectrum thus was modeled as independent variable, allowing analysis of deviation from linearity.

Continuity and discontinuity in the pattern of associations were tested by modeling spectrum as linear effect and assessing the effect of adding a squared term of spectrum. A nonsignificant squared term suggests continuity (no deviation from linearity), a negative squared term suggests a qualitatively stronger association at the lower end of the psychosis spectrum, and a positive squared term suggests a qualitatively stronger association at the higher end of the psychosis spectrum (figure 1).

The layout of the results in the tables is as follows. For each demographic (table 1), psychopathological (table 2), or etiological (table 3) variable, results were depicted in the corresponding table row, showing (1) the OR for association with the 5 groups of the spectrum variable (with absence of psychosis as the reference group, ie OR = 1), (2) whether or not the association deviated form linearity and, if so, deviation was positive or negative (figure 1), and (3) the test for significance for deviation from linearity.

Results

Sample Description

Mean age of the sample was 37.4 years, 42.0% were men, and 26.7% were of non-Turkish origin. Distributions of demographic, psychopathological, and etiological variables per level of the psychosis spectrum variable are displayed in tables 1–3.

Demographic Variables and Psychosis Continuity

There were dose-response linear associations between the 5 groups of increasing clinical severity of psychosis and indices of premorbid social adjustment (single marital status and unemployment; table 1). At the highest end of the clinical spectrum, women were more likely to remain at the level of high-impact psychotic symptoms, whereas men were more likely to progress to disorder level. Younger age was associated with psychosis below the level of disorder but not with psychotic disorder (table 1).

Psychopathology and Psychosis Continuity

There were dose-response linear associations between the 5 groups of increasing clinical severity of psychosis and the rate of hallucinations with copresence of delusions (table 2). There were dose-response but extralinear associations—indicating disproportionately strong association at the clinical disorder end of the spectrum—with number of psychotic symptoms (both delusions and hallucinations), negative symptoms, symptoms of disorganization, and interviewer impression of mental illness. Factors with an extralinear pattern of association with stronger impact below the level of clinical disorder were affective symptoms (both mania and depression; table 2).

Etiology and Psychosis Continuity

There were dose-response linear associations between the 5 groups of increasing clinical severity of psychosis and urbanicity, childhood adversity, a history of mental illness in a single relative, and a family history of common mental disorder (table 3). There were dose-response but extralinear associations—indicating disproportionately stronger associations at the clinical disorder end of the spectrum—with cannabis use, family history in more than 1 relative, and family history of SMI (table 3).

Discussion

As far as we are aware, this is the first investigation examining positions over a hypothesized continuum of psychosis, defined in terms of the spectrum of clinical severity, in relation to demographic, psychopathological,

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Table 1. Distribution of Demographic Variables Per Category of Outcome and Regression Results

	Absence Psychosis, n = 2980		Subclinical Psychotic Experience, n = 625		Low-Impact Psychotic Symptoms, n = 198		High-Impact Psychotic Symptoms, n = 109		Clinical Psychotic Disorder, n = 99		Deviation From Linearity		
	n (%)	OR[a]	n (%)	OR (95% CI)[a]	n (%)	OR (95% CI)[a]	n (%)	OR (95% CI)[a]	n (%)	OR (95% CI)[a]	Direction[b]	χ^{2d}	P-value
Female	1728 (58)	1 (ref)	345 (55)	0.9 (0.8–1.1)	124 (63)	1.3 (0.94–1.70)	80 (74)	2.1*** (1.4–3.3)	51 (52)	0.77 (0.52–1.15)	0	0.27	.61
Non-Turkish	770 (26)	1 (ref)	184 (29)	1.2 (0.99–1.45)	49 (25)	0.96 (0.69–1.34)	36 (33)	1.5 (0.97–1.34)	31 (31)	1.3 (0.8–2.0)	0	0.21	.65
Single or divorced	772 (26)	1 (ref)	239 (38)	1.4** (1.1–1.7)	75 (38)	1.5** (1.1–2.2)	39 (36)	1.6* (1.01–2.5)	47 (47)	3.2** (2.0–5.1)	0	0.53	.47[e]
Unemployed	131 (4)	1 (ref)	41 (7)	1.3 (0.9–1.9)	14 (7)	1.6 (0.9–2.9)	10 (9)	2.6** (1.3–5.2)	12 (12)	2.9** (1.5–5.5)	0	1.47	.23
	Mean (SD)	B[a]	Mean (SD)	B (95% CI)[a]	Mean (SD)	B (95% CI)[a]	Mean (SD)	B (95% CI)[a]	Mean (SD)	B (95% CI)[a]			
Age	38.3 (13.3)	0 (ref)	34.4 (13.3)	−3.9*** (−5.0 - −2.8)	34.5 (13.0)	−3.8*** (−5.8 - −1.9)	35.4 (13.1)	−3.1* (−5.7 - −0.58)	37.6 (12.5)	−0.53 (−3.2 - 2.1)	+	33.8	<.0001
Socioeconomic status	2.59 (1.18)	0 (ref)	2.73 (1.10)	0.13** (0.04–0.2)	2.83 (1.10)	0.23** (0.06–0.40)	3.08 (1.06)	0.47*** (0.25–0.69)	3.01 (1.06)	0.42*** (0.19–0.65)	0	0.19	.66
Drop in class[c] as compared with father	0.29 (0.58)	0 (ref)	0.25 (0.55)	−0.02 (−0.08 - 0.02)	0.37 (0.68)	0.09 (−0.0001 - 0.17)	0.38 (0.64)	0.09 (−0.03 - 0.20)	0.39 (0.65)	0.10 (−0.02 - 0.22)	0	1.08	.30

[a]Adjusted for age category (15–24, 25–34, 35–44, 45–54, and 55–64 years) and sex.
[b]Direction: "+" indicates positive extralinear effect, "−" indicates negative extralinear effect, and "0" indicates no evidence for deviation from linearity.
[c]Socioeconomic status of both subject and of father in 4 categories (1: I and II professional and IIIA nonmanual high employee, 2: IIIB nonmanual low employee and V and VI skilled workers and technicians, 3: IVA, IVB, and IVC small proprietors with or employee, and (4 VIIA and B manual workers).
[d]$df = 1$.
[e]Excluding the 15- to 24-year-olds but including both age and sex as confounders in the analysis.
*$P < .05$, **$P < .01$, ***$P < .001$.

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Table 2. Distribution of Symptoms Per Category of Outcome and Regression Results

	Absence Psychosis, n = 2980		Subclinical Psychotic Experience, n = 625		Low-Impact Psychotic Symptoms, n = 198		High-Impact Psychotic Symptoms, n = 109		Clinical Psychotic Disorder, n = 99		Deviation From Linearity		
	n (%)	OR[a]	n (%)	OR (95% CI)[a]	n (%)	OR (95% CI)[a]	n (%)	OR (95% CI)[a]	n (%)	OR (95% CI)[a]	Direction[b]	χ^{2c}	P-value
Both hallucinations and delusions	0 (0)	n.a.	71 (11.3)	1 (ref)	77 (39.1)	5.0*** (3.4–7.4)	57 (52.8)	8.4*** (5.3–13.3)	79 (79.8)	37.7*** (21.3–66.7)	0	0.18	.7
Negative symptoms	104 (3.5)	1 (ref)	48 (7.7)	2.18*** (1.52–3.11)	29 (14.7)	4.60*** (2.96–7.15)	22 (20.4)	6.91*** (4.15–11.5)	49 (49.5)	27.2*** (17.5–42.2)	+	18.5	<.0001
Disorganization	24 (0.8)	1 (ref)	10 (1.6)	2.12* (1.003–4.5)	7 (3.6)	4.8*** (2.03–11.3)	7 (6.5)	9.1*** (3.80–21.7)	25 (25.3)	42.3*** (23.0–77.9)	+	19.2	<.0001
Interviewers impression that subject is mentally ill	9 (0.3)	1 (ref)	5 (0.8)	2.6 (0.8–7.8)	14 (7.1)	25.0** (10.7–58.8)	8 (7.4)	26.7*** (10.0–71.2)	26 (26)	116*** (52.6–257)	+	30.5	<.0001
	Mean (SD)	B[a]	Mean (SD)	B (95% CI)[a]	Mean (SD)	B (95% CI)[a]	Mean (SD)	B (95% CI)[a]	Mean (SD)	B (95% CI)[a]			
Number of delusions or hallucinations	0 (0)	0 (ref)	1.47 (0.88)	1.5*** (1.4–1.5)	2.27 (1.42)	2.3*** (2.2–2.4)	3.36 (2.18)	3.3*** (3.2–3.5)	6.05 (3.17)	6.1*** (5.9–6.2)	+	29.63	<.0001
Number of delusions	0	0 (ref)	1.13 (0.82)	1.1*** (1.06–1.2)	1.23 (1.22)	1.2*** (1.1–1.3)	1.98 (1.65)	2.0*** (1.8–2.1)	4.10 (2.70)	4.1*** (4.0–4.2)	+	11.59	.0007
Number of hallucinations	0	0 (ref)	0.34 (0.62)	0.34*** (0.30–0.38)	1.04 (0.91)	1.0*** (0.98–1.1)	1.38 (1.34)	1.37*** (1.28–1.45)	1.95 (1.33)	1.95*** (1.87–2.04)	+	20.12	<.0001
Depression sum score	1.1 (2.4)	0 (ref)	2.5 (3.3)	1.37*** (1.14–1.61)	3.9 (3.7)	2.69*** (2.30–3.08)	5.5 (3.7)	4.27*** (3.75–4.79)	4.4 (3.8)	3.36*** (2.81–3.90)	−	22.8	<.0001
Mania sum score	0.06 (0.5)	0 (ref)	0.3 (1.4)	0.22*** (0.13–0.31)	0.7 (2.2)	0.58*** (0.43–0.73)	1.1 (2.7)	1.02*** (0.82–1.23)	0.6 (2.3)	0.54*** (0.33–0.75)	−	6.39	.01

[a]Adjusted for age category (15–24, 25–34, 35–44, 45–54, and 55–64 years) and sex.
[b]Direction: "+" indicates positive extralinear effect, "−" indicates negative extralinear effect, and "0" indicates no evidence for deviation from linearity.
[c]$df = 1$.
*$P < .05$, **$P < .01$, ***$P < .001$.

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Table 3. Distribution of Etiological Variables

	Absence Psychosis n = 2980		Subclinical Psychotic Experience n = 625		Low-Impact Psychotic Symptoms n = 198		High-Impact Psychotic symptoms n = 109		Clinical Psychotic Disorder n = 99		Deviation From Linearity		
	n (%)	OR[a]	n (%)	OR (95% CI)[a]	n (%)	OR (95% CI)[a]	n (%)	OR (95% CI)[a]	n (%)	OR (95% CI)[a]	Direction[b]	χ^{2d}	P-value
Mental illness in 1 family member[c]	398 (13.7)	1.00 (ref)	111 (18.5)	1.45** (1.14–1.83)	31 (16.9)	1.28 (0.86–1.92)	24 (26.0)	2.18** (1.35–3.52)	23 (29.1)	2.62*** (1.59–4.31)	0	0	.98
Mental illness in >1 family member[e]	84 (3.3)	1.00 (ref)	28 (5.4)	1.78* (1.14–2.77)	14 (8.4)	2.77** (1.5–5.0)	16 (19.1)	6.5*** (3.6–11.7)	20 (26.3)	12.0*** (6.8–21.1)	+	8.48	.004
FH common mental disorder	428 (14.6)	1.00 (ref)	125 (20.4)	1.50*** (1.20–1.88)	36 (19.2)	1.37 (0.96–2.0)	35 (34.0)	2.88*** (1.9–4.4)	26 (31.7)	2.8*** (1.7–4.5)	0	0	1.0
FH severe mental illness	54 (2.1)	1.00 (ref)	14 (2.8)	1.47 (0.81–2.68)	9 (5.6)	2.92** (1.41–6.1)	5 (6.9)	3.62** (1.39–9.42)	17 (23.3)	15.4*** (8.3–28.5)	+	8.65	.003
At least 1 childhood adverse life event	404 (13.6)	1.00 (ref)	109 (17.4)	1.4** (1.1–1.8)	42 (21.3)	1.8** (1.3–2.6)	25 (23.2)	2.0** (1.3–3.2)	25 (25.3)	2.2** (1.4–3.5)	0	0.97	.32
Cannabis	19 (0.6)	1.00 (ref)	8 (1.3)	1.63*** (0.70–3.77)	11 (5.6)	9.8*** (4.5–21.6)	6 (5.6)	15.0*** (5.5–41.0)	13 (13.1)	26.8*** (12.1–59.3)	+	6.18	.01
Urbanicity at birth[g]											0	0.17	.68
Village or district population <50 000	1313 (46.3)	1.00 (ref)	236 (38.8)	1.14 (0.95–1.37)	66 (35.1)	1.41* (1.04–1.91)	47 (44.3)	1.10 (0.73–1.64)	37 (40.0)	1.65* (1.08–2.53)			
50 000–200 000	366 (12.9)		81 (13.3)		25 (13.3)		12 (11.3)		6 (6.5)				
Province >200 000	122 (4.3)		26 (4.3)		10 (5.3)		6 (5.7)		3 (3.2)				
District in metropolitan area	1038 (36.6)		265 (43.6)		87 (46.3)		41 (38.7)		47 (50.5)				
Urbanicity aged 6–15 years[g]											0	0.10	.75
Village or district population <50 000	846 (29.2)	1.00 (ref)	147 (23.9)	1.11 (0.91–1.34)	38 (19.7)	1.44* (1.03–2.00)	29 (26.9)	1.11 (0.74–1.69)	20 (20.6)	2.02** (1.24–3.29)			
50 000–200 000	283 (9.8)		57 (9.3)		18 (9.3)		9 (8.3)		3 (3.1)				
Province >200 000	154 (5.3)		23 (3.7)		11 (5.7)		2 (1.9)		7 (7.2)				
District in metropolitan area	1618 (55.8)		388 (36.1)		126 (65.3)		68 (63.0)		67 (69.1)				

Note: FH, family history.
[a]Adjusted for age category (15–24, 25–34, 35–44, 45–54, and 55–64 years) and sex.
[b]Direction: "+" indicates positive extralinear effect, "−" indicates negative extralinear effect, and "0" indicates no evidence for deviation from linearity.
[c]If in more than 1 family member: excluded.
[d]$df = 1$.
[e]If in 1 family member: excluded.
[g]In logistic regression, ≤200 000 = 0 and >200 000 = 1.
*$P < .05$, **$P < .01$, ***$P < .001$.

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and etiological variables. The pattern of results was that demographic variables, indicative of premorbid social adjustment and socioeconomic status, impacted mostly linearly; proxy variables of genetic risk impacted in a positive extralinear fashion if associated with more affected relatives or more severe illness in the family; environmental risk factors sometimes impacted linearly (urbanicity and childhood adversity) and sometimes extralinearly (cannabis), occasioning a disproportional shift in risk at the clinical disorder end of the spectrum. Interestingly, associations with psychopathological variables provided the clearest contrast, in that, affective symptoms were associated with a disproportionally higher risk below the disorder end of the spectrum, whereas a disproportionally higher risk at the disorder end of the spectrum was associated with psychotic symptom load, negative symptoms, disorganization, and visible signs of mental illness. In agreement with previous work[9] was the observation that the greater the degree of delusional "comorbidity" with hallucinations, the greater the risk (in a linear fashion) with more severe outcome over the psychosis spectrum. The shift toward better outcomes for women at the clinical end of the spectrum is also in line with previous work in this area: Definitions of psychotic disorder focusing on negative symptoms and longer duration (associated with poorer outcome) show higher incidence rates for men,[34] whereas for definitions allowing for the inclusion of more affective symptoms and brief presentations (associated with better outcome), the gender ratio is closer to unity.[35,36] These data suggest that the symptomatic expression of liability for psychotic disorder is more severe for men compared with women. Such differences have been explained in terms of underlying differences in neurodevelopment, alterations of which may be more common in men.[37] The association with younger age is in line with meta-analytical work in this area;[1] the reason this association was not apparent at the disorder level is to be expected because associations were calculated with current age rather than age at onset in a prevalence sample of patients with existing disorder.

Previous Work

Although the current study is cross-sectional in nature and therefore does not inform on likelihood of transition from subclinical to clinical psychotic outcome, the nature of the cross-sectional associations over the continuum of psychosis is in agreement with the epidemiological literature on follow-up studies of representative general population cohorts with psychotic experiences and the factors that moderate transition to a clinical psychotic outcome. These studies have demonstrated that shifts from nonclinical to clinical outcomes of psychosis are associated with the number and severity of symptoms,[11–13,38] the degree to which hallucinations present with comorbid delusional ideation[9] and negative disorganized symptoms.[39] There is apparent disagreement with another study showing that greater degree of affective dysregulation also predicted transition to clinical outcome;[14] however, the clinical outcome in that study overlapped with level 3 of the spectrum variable in the current study (high-impact psychotic symptoms) that displayed the strongest association with both depressive and manic affective comorbidity. The contribution of the current study is that many of these psychopathology and symptom loading factors associated with transition do so in an extralinear fashion, with disproportional increases in risk either below or at the severest end the spectrum. In addition, the current study suggests that some etiological factors, such as cannabis, show similar disproportionate increases in risk toward the disorder end of the spectrum.

The lack of ethnic differences in this study is interesting and in agreement with earlier work showing that an important underlying mechanism may be the degree of "standing out" of an ethnic group in relation to the majority ethnic group environment.[40] The current results are in agreement with this observation because the ethnic groups under examination share the same religion and cannot be distinguished on the basis of appearance, skin color, or daily life behavior.

How to Explain Disproportional Increases or Decreases in Risk Over the Spectrum?

Disproportional increases or decreases in risk at the clinical end of the spectrum of psychosis do not necessarily represent evidence of discontinuity. For example, the OR for negative symptoms increased over the 5 levels of the psychosis spectrum variable from 1, 2.2, 4.6, 6.9 to a disproportionally high OR of 27.2 for the highest level of psychotic disorder, and for cannabis, these ORs were, respectively, 1, 1.6, 9.8, 15.0, and 26.8. The pattern of evolution of risk over the spectrum clearly shows continuous increase in risk, suggesting underlying continuity in association; what is discontinuous is the degree of extralinearity associated with the increase at or below the disorder end of the spectrum. It has been suggested that this type of relationship may be called quasi-continuous[8] and can be understood as effects by unmeasured moderators that give rise to qualitative differences at the end of the continuum.[8] Statistical simulations indeed show that the skewed distribution of quasi-continuous traits can be reduced to underlying multifactorial etiology with multiple factors strongly interacting with each other.[1,41] Thus, the results are compatible with a model of common etiological factors occasioning expression of psychotic experiences and affective dysregulation and interactions with less common etiological factors occasioning increasing admixture with poor outcome symptomatology such as negative symptoms, disorganization and, possibly—because it was not measured in the current investigation—cognitive impairment. Given the fact that greater familial

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loading with common mental disorder (ie, multiple affected relatives) and loading with more severe mental disorder were associated with extralinear increases in risk toward the clinical end of the spectrum, it may be hypothesized that some of the interacting factors are genetic. Interestingly, previous research suggests that, although the relative risks are highest for a (low prevalent) family history of psychotic disorder, more psychotic disorder is attributable, at the population level, to (high prevalent) nonpsychotic illness than to psychotic disorder.[42] The current analysis shows that the origin of these effects can be traced to a linear increase in risk over the clinical spectrum of psychosis associated with common mental disorder and an extralinear increase in risk associated with SMI. In other words, high prevalent and low prevalent genetic risks for psychotic disorder, in interaction with environmental risks, may operate by impacting differentially over an extended psychosis phenotype that is distributed in the general population and can be operationalized as a continuum of clinical severity.

Methodological Issues

The results need to be considered in the light of the following considerations. First, the notion of a continuum can be conceptualized in many ways. The current choice to define the concept of a continuum in terms of a spectrum of clinical severity is arbitrary and could be replaced by, eg, a spectrum based on number and/or type of symptoms or indeed multiple dimensions of different symptom domains. We chose for a clinical operationalization of the psychosis continuum, based on progressive impairment; this choice ensured a degree of clinical validity of the findings, which arguably should be the leading perspective. Second, the choice to examine statistical aspects of extralinearity on the additive scale is (ie, the scale where the difference between a group with 25% risk and a group with 10% risk is expressed as a risk difference of 15% rather than a risk ratio of 2.5), to a degree, arbitrary and was motivated by findings indicating that natural synergism between risk factors underlying multifactorial phenotypes can be approached better from additive statistical models.[43] Nevertheless, there is no certainty about which statistical scale corresponds to natural effects, and this limitation is important for all psychiatric research. Third, the assessment of psychosis in the general population inevitably is associated with a degree of misclassification (false positives and false negatives).[3] However, although this undoubtedly was the case in the current investigation, there is little reason to assume that misclassification was differential with regard to the demographic, psychopathological, and etiological variables on the one hand and the psychosis spectrum variables on the other; therefore, it is unlikely to have biased the findings.

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