

Shades of vulnerability: latent structures of clinical caseness in prodromal and early phases of schizophrenia

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Abstract The underlying structures of clinical caseness and need of care in prodromal (i.e., at-risk) and early phases of schizophrenia remain poorly characterized in their essential psycho-behavioral coherence. To identify the schizophrenia proneness-related subtypes within a population of young help-seekers referred to a dedicated, community-based early detection program (Programma 2000). A sample of consecutive referrals ($n = 168$) for suspected psychosis or first-episode schizophrenia spectrum psychosis received a detailed clinical assessment, including the early recognition inventory for the retrospective assessment of the onset of schizophrenia checklist. We used exploratory factor analysis (EFA) to determine the underlying dimensional structure and latent class analysis (LCA) to identify putative vulnerability subtypes. EFA identified four factors: dysphoria (irritability tension), paranoid aut centrism, introversive withdrawal, and disturbed subjective experience. LCA distinguished three classes, interpretable as carrying different degrees of

“proneness to schizophrenia psychosis,” which best captured the underlying continuum of clinical severity. The validity of the three classes was supported by distinct patterns of association with major clinical variables (i.e., diagnostic staging at referral). Vulnerability to schizophrenia psychosis in young help-seekers may manifest in three major clinical prototypes, presenting common levels of dysphoria and social withdrawal but different degrees of paranoid aut centrism and disturbed subjective experience. Overall, the results provide the empirical background to dissect shared features of clinical caseness from more schizophrenia-specific vulnerability components. This is of value for the refinement of the clinical staging model as well as for the pragmatic implementation of multiple-gate screening programs.

Keywords Psychosis · Schizophrenia · Prodrome · Staging · Clinical high risk · Early intervention

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Introduction

The overarching goal of this study is to derive a parsimonious, clinically interpretable model of vulnerability to schizophrenia that could help differentiate between early and milder clinical phenomena (related to initial help-seeking) from those that accompany illness progression, and possible progression toward diagnostically more severe conditions, already at the first referral. Such a model could have both heuristic and translational use. The heuristic use would be aimed at deriving empirically based prototypes of vulnerability to schizophrenia from the “in vivo” presentations of help-seeking subjects in a naturalistic treatment context; the translational use would provide helpful resources for the initial staging of vulnerability that could be implemented at the entry of a multiple-gate screening strategy.

The study, which is based on the data collected in a real-world setting of the Italian mental health services, is conceived according to the conceptual frame of contemporary prodromal/clinical high-risk paradigm and adopts a pragmatic perspective to the continuum of the need of care [1–3]. Within this perspective, all the appropriate referrals to a dedicated early intervention program (Programma 2000, Milan, Italy) were regarded as expressive of increasing degrees of need of care according to their treatment admission state, which ranged from putatively prodromal phase to early schizophrenia up to 2 years since the onset [4, 5].

Background and rationale

The prodromal or clinical high-risk (CHR) paradigm has become a widely adopted frame for investigating the onset of schizophrenia and related psychotic disorders [6, 7]. Conceptually, this paradigm complements the genetic, familial high-risk (FHR) approach and focuses on help-seeking young adults who are at putative risk of incipient and frankly symptomatic psychosis [8–12].

Current definitions of the early-risk stages of schizophrenia and related psychotic disorders include: sub-threshold psychotic symptoms (in the form of attenuated and/or transient positive symptoms), self-experienced vulnerability (i.e., at-risk basic symptoms) [13], as well as a combination of genetic risk (e.g., diagnosis of schizotypy or positive family history for schizophrenia or psychosis) associated with a recent deterioration in global functioning [6, 10, 14–18]. The identification of such states is relevant for the purposes of rational decision making as well as for the delivery of symptom/need-based interventions through the network of community services. However, despite the profusion of criteria and available assessment instruments [19], the need for care in prodromal patients remains

poorly characterized in their clinical, psycho-behavioral coherence [17, 20, 21].

We think that a more fine-grained definition of the levels of psycho-behavioral coherence that characterize prodromal versus early phases of schizophrenia could be important to optimize hierarchical risk enhancement in the first-contact settings. [22–24].

Study design and aims

The current protocol is based on the data collected over a decade (1999–2009) in the first Italian multi-modal early detection treatment program (Programma 2000). Programma 2000 was originally conceived as a pilot experience to implement the emerging international paradigms of early detection within the framework of the community-based, Italian mental health network of care [4]. It was established at the end of the 1990s, to intercept a variety of help-seeking needs related to the prodromal and early phases of schizophrenia and offer specific assessment and therapeutic support to cases otherwise dispersed in the network of standard adult mental health services [4, 5].

The background idea was to integrate the rapidly expanding knowledge in the field of early detection by adapting the CHR framework to the already available therapeutic infrastructures of the Italian community mental health services.

In this study, we aimed at exploring the continuum of help-seeking needs across a wide spectrum of referrals (from putatively prodromal to early phases of schizophrenia psychosis), as naturalistically intercepted in a specialized community-based setting. To this purpose, we tested the early recognition inventory for the retrospective assessment of the onset of schizophrenia checklist (ERIRAOS-CL) as a clinical probe to systematically map basic vulnerability features across the help-seeking young adults. The ERIRAOS-CL is a 17-item checklist designed to assist the exploration of individual proneness to schizophrenia, thereby optimizing the initial risk assessment within multiple-gate screening mental health pathways [24]. The ERIRAOS-CL capitalizes on the results of the ABC Schizophrenia Study, a large-scale European epidemiological project, designed to analyze the early course of schizophrenia from the onset until first contact in view of its impact on course and outcome, and explores a variety of psycho-behavioral manifestations of growing specificity [25, 26]. These include—among others—social withdrawal, depression, loss of energy, nervousness, thought pressure, derealisation, persecutory ideation, and hallucinations. The frequency of these manifestations increases along the progression of the prodromal phase [26] (See “Appendix” for details).

In this study, we explored both dimensional and taxonomic features of psychopathological vulnerability (as detected by the ER/raos-CL) and compared them with the actual clinical diagnostic staging at referral (i.e., putative prodrome or early phase of schizophrenia psychosis). We tested the hypothesis that common features among help-seeking young adults would correspond to a background, shared clinical expression of symptoms, i.e., a rather broad maladaptive manifestation of distress motivating the specialized referral, while specific differences would be indicative of a more selective vulnerability to schizophrenia (i.e., schizophrenia proneness).

Methods

Participants and setting

Programma 2000 is a multi-modal, community-based program on early intervention in psychosis settled in Italy, Milan, since 1999. The service was originally implemented as a pilot experience to test emerging international practices in the field within the specific context of the Italian mental health system. This is an integrated, community-oriented network of mental health services, which gradually replaced asylum-based psychiatric treatments since the law-enforced deinstitutionalization in 1978 [27–29].

Programma 2000 operates under constant international supervision and consultation as an assessment and treatment hub for several referral agencies, ranging from institutionally mediated pathways (e.g., primary care, district MH, school counseling, emergency rooms) to spontaneous help-seeking individuals (e.g., self-referrals or family referrals in response to awareness campaigns). The served catchment area includes approximately 200,000 inhabitants.

Criteria for referral and preliminary evaluation are as follows: age between 17 and 30 years and help-seeking for early or impending psychosis.

After the assessment, the admission to the Programma 2000 treatment protocol is offered to subjects in a CHR state or in the early phase of a schizophrenia or related psychotic disorder, conventionally termed first-episode psychosis (FEP) (details in [4, 5]).

CHR states are defined according to the criteria of the Early Detection and Intervention program of the German Research Network on Schizophrenia (GRNS) [24, 30]. These enlist four potential state configurations characterized by: (a) self-experienced cognitive thought and perception disorders (“basic symptoms” according to [31]); (b) putative genetic vulnerability (e.g., family history of psychosis) with recent functional decline; (c) attenuated

positive symptoms; (d) brief, limited, and intermittent psychotic symptoms.

Criteria “a” and “b” define the so-called early initial prodromal state (EIPS), whereas condition “c” and “d” are associated with higher risk of imminent transition to psychosis and termed “late initial prodromal state” (LIPS) [15, 32]. Criteria “b,” “c,” and “d” are substantially similar to the “ultra-high-risk” (UHR) criteria proposed by the Personal Assessment and Crisis Evaluation (PACE) Clinic in Melbourne [9, 33, 34]; see [6] for an overview and [16, 17] for further discussion.

FEP is operatively defined as a diagnosis of schizophrenia or related syndromes (such as F20-29 in ICD-10) according to the ICD-10 [35], with duration of untreated psychosis (DUP) less than 24 months. The majority of this group includes subjects referred to Programma 2000 immediately after a first contact with any public mental health service of the catchment area and contextually diagnosed as suffering from non-affective psychosis prior to admission.

Exclusion criteria in both groups are as follows: comorbid medical or neurological disorders; affective psychosis (bipolar disorder, or unipolar disorder with psychotic features); persistent substance-use-dependent disorder. Subjects with substance use/abuse but without dependence are eligible for treatment.

Since its foundation (January 1999) up to September 2009, a total of 404 subjects have been referred to the service for preliminary assessment. Of those, 368 (91 %) were compatible with the eligibility criteria as listed beforehand (CHR or FEP) and underwent a preliminary screening. About one-third ($n = 127$) resulted as non-appropriate referrals (78 did not meet the clinical high-risk threshold, whereas 49 had a DUP above 24 months); in 11 cases, the assessment was not completed; 44 met the admission criteria, yet they were living in other regions of Italy and therefore referred back to the competent district service. Out of a total of 186 subjects who were offered a dedicated 5-year protocol of care, 89 % ($n = 167$) accepted. Of those, 81 were CHR and 86 FEP.

The data analyzed in the current report were collected as part of the routine clinical assessment, after informed consent from the clients and study approval from the institutional review board.

Clinical assessment

Programma 2000 assessment scheme (see [4, 5] for details) includes standard, internationally recommended measures [such as the Brief Psychiatric Rating Scale (BPRS), the global assessment of functioning (GAF), and the Health of the Nation Outcome Scale (HoNOS)] as well as a dedicated instruments for the screening of at-risk states, the

ERiraos-CL [25, 26, 36]. The ERiraos-CL is a 17-item, interview-based tool that encompasses a broad range of progressively severe and characteristic prodromal phenomena (such as social withdrawal, depressive mood, tension, derealization, changes in perceptual and thought experience, hallucinatory-like experiences). The sequence of symptoms assessment, starting with unspecific symptoms, followed by basic symptoms and psychotic indicators, is meant to reconcile a good flow of the interview within a focused, non-intrusive exploration of relevant clinical domains (see “Appendix” for details).

The ERiraos-CL is designed to facilitate assessment also in non-specialized settings, serving as a suitable tool for early screening in a multiple-gate process of risk identification.

For the purpose of the statistical analysis, we dichotomized ERiraos-CL item scores as follows: “absent”/“doubtfully present” was coded 0 (absent) and “definitely present” was coded 1 (present).

All the scales (BPRS, GAF, HoNOS, and ERiraos-CL) are part of standard assessment both at admission and at follow-up. Inter-rater agreement among the clinical staff is regularly checked to insure good-to-acceptable concordance on the scales; intra-class correlation coefficients were .70 or above in all scales when carried on in a small sample of patients ($n = 25$) during training; k-agreement for GAF was .80 in training.

Statistical analyses

All data were coded and analyzed using the Statistical Package for Social Sciences (SPSS) for Windows (Chicago, Illinois 60606, USA), version 13. All tests were two-tailed, with statistically significant threshold set at $p = .05$. Categorical data were analyzed in inter-group comparisons with χ^2 , or Fisher’s exact test, when appropriate ($n < 5$ in any cell in binary comparison). Student’s t test or the Mann–Whitney test, when appropriate, was used to compare the ordinal variables.

Construct validity was assessed with exploratory factor analysis (EFA). Factor analysis was carried out by unweighted least squares, with polychoric correlations due to the dichotomous nature of the items. We applied parallel analysis using marginally bootstrapped samples ($n = 500$) to extract factors with eigenvalues higher than 1, retaining only those that were statistically higher than the mean of random eigenvalues generated by bootstrapping. Promax rotation was applied to the data. Promax rotation applies a Varimax rotation to the data and then forces the solution to a target allowing the inter-correlation of the extracted factors, as awaited on the basis of the ERiraos-CL construct. The root mean square of residuals (RMSR) and its ratio to the expected mean value of

RMSR was used to assess fitness of the model; good fit is assumed for $\text{RMSR} \leq .05$, with the value of RMSR being lower than the expected mean value of RMSR. Bentler’s [37] simplicity index and the reliability estimate of the extracted components were also used to assess adequacy of the model [38]. We used FACTOR to generate these analyses [39].

To test the association of the dimensions extracted by factor analysis and diagnostic status at referral, we used the multivariate analysis of covariance (MANCOVA), entering factor scores as outcome: diagnostic staging groups (CHR vs FEP) were entered as predictors with age and gender as covariates.

Latent class analysis (LCA) was used to derive a typology of schizophrenia psychosis proneness from the endorsement patterns of the ERiraos-CL items, each item addressing different prodromal manifestations. Indeed, whereas factor analysis identifies unobserved common dimensions accounting for the correlations among observed variables, LCA identifies (latent) subgroups of individuals (i.e., classes) who share common features (in this case, ERiraos-CL features). Briefly, LCA posits that a heterogeneous group can be reduced to several homogeneous subgroups by evaluating and then minimizing the associations among responses across multiple variables and tests for the existence of discrete groups with a similar symptom or item endorsement profile [40, 41].

Latent class analysis estimates two parameters: (1) the likelihood of endorsement of a given item (in this case, ERiraos-CL’s items) for individuals in a particular class and (2) the class membership probabilities. Since in LCA no a priori assumptions are made concerning the number of latent classes, LCA model selection was conducted according to fitting indices such as likelihood ratio [$-2 \times \text{Ln}(L)$], the Akaike information criterion (AIC) [42], the Bayesian information criterion (BIC) [43], and the sample size-adjusted BIC (SSABIC) [44]. For each of these indexes, lower values indicate better fit. The Lo-Mendell-Rubin’s adjusted likelihood ratio test (LRT) [45] was also used to compare models with different number of latent classes. Standardized entropy measure was used to assess accuracy in participants’ classification (values range 0–1), with higher values indicating better classification.

Finally, multinomial logistic regression was used to assess the association between classes’ membership and demographic (i.e. gender and age) or clinical variables (diagnosis at referral).

Results

General characteristics of the sample were summarized in Table 1.

Table 1 Baseline characteristics of patients included in the study (individuals enrolled from January 1999 until September 2009)

All values: no. (%) or mean (SD)	Total sample (<i>n</i> = 167)	First-episode psychosis (<i>n</i> = 86)	Clinical high-risk subjects (<i>n</i> = 81)	Statistics
Age at entry	22.5 (3.7)	22.6 (3.8)	22.3 (3.6)	$t = -.58$, $df = 165$, $p = .56$
Gender (<i>n</i> , % of males)	126 (75.4)	69 (80.2)	57 (70.4)	$\chi^2 = 1.69$, $df = 1$, $p = .19$
Age of males	22.2 (3.7)	22.3 (3.7)	22.0 (3.7)	
Age of females	23.3 (3.8)	23.7 (4.3)	23.0 (3.5)	
Education				$\chi^2 = .81$, $df = 2$, $p = .66$
College graduate or higher	10 (6.0 %)	6 (7.0 %)	4 (4.9 %)	
High school diploma	77 (46.1 %)	37 (43.0 %)	40 (49.4 %)	
Lower than high school diploma	80 (47.9 %)	43 (50.0 %)	37 (45.7 %)	
Family psychiatric history				$\chi^2 = 1.29$, $df = 1$, $p = .25$
First-/second-degree relative with psychosis	25 (14.9 %)	16 (18.6 %)	9 (11.1 %)	
History of severe obstetric complications	39 (23.3 %)	20 (23.2 %)	19 (23.4 %)	$\chi^2 = .01$, $df = 1$, $p = 1.00$
Duration of untreated psychosis (days)	168.8 (217.5)	168.8 (217.5)	–	–
Duration of untreated illness (months)	29.1 (21.1)	28.4 (20.4)	29.9 (21.9) ^c	Mann–Whitney $z = -.25$, $p = .79$
Clinical characteristics at enrollment				
ERIraos-CL	22.7 (8.8)	26.5 (8.1)	18.2 (7.6)	Mann–Whitney $z = -5.68$, $p = .0001$
HoNOS, total score ^a	14.2 (6.0)	15.3 (6.7)	13.0 (4.9)	Mann–Whitney $z = -2.61$, $p = .009$
BPRS, total score	49.2 (15.1)	53.3 (17.0)	44.8 (11.4)	Mann–Whitney $z = -3.43$, $p = .001$
GAF ^b	48.2 (10.4)	43.7 (9.0)	52.9 (9.6)	Mann–Whitney $z = -6.09$, $p = .0001$

^a In 12 patients the data was lacking

^b In 11 patients the data was lacking

^c DUI, here, refers to the interval between the onset of unspecific symptoms recognized by the patient and the actual referral to a specific treatment facility

There was a preponderance of male patients, and a large fraction of the enrolled patients had a family history of psychopathology, principally a first-/second-degree relatives diagnosed with psychosis or an affective disorder. No relevant sociodemographic differences were found across the two diagnostic staging subgroups, CHR and FEP. As expected on the basis of the definition, FEP patients were more severe in terms of clinical measures (Table 1).

Factorial analysis

In EFA, the best fit was for a four-factor solution: eigenvalues of four factors only were higher than 1 and contemporarily higher than the random eigenvalues generated by bootstrapping; RMSR was .041, and it was lower than the expected mean value of RMSR = .075. Finally, Bentler's simplicity index was .97, close to 1, and all reliability estimates of the extracted factors were good, while in the five-factor solution, one factor had a

reliability estimate lower than the suggested threshold of .70 (data available on request), and the Bentler's simplicity index (.94) was lower than the value observed in the four-factor solution.

The factors were tentatively labeled, according to the item loadings, as follows: “dysphoria” (tension, irritability), “paranoid aut centrism” (self-reference, suspiciousness), “introvertive withdrawal” (social withdrawal, shyness), and “disturbed subjective experience” (derealization, changes in perception) (Table 2).

The extracted factors were poorly interrelated with each other, thus allowing independent discrimination between the explored dimensions; only “paranoid aut centrism” factor was highly correlated ($r = .29$, $p < .0001$) with the “disturbed subjective experience” factor.

High scores on “paranoid aut centrism” and “disturbed subjective experiences” dimensions were predicted by the diagnostic grouping (FEP > CHR), whereas there were no differences with regard to the other two components

Table 2 Factor solution of the ERiraos-CL (total sample)

	Factor 1 dysphoria	Factor 2 paranoid autocentrism	Factor 3 disturbed subjective experience	Factor 4 introversive withdrawal
1. Social withdrawal				.858
2. Shyness				.717
3. Depressive mood	.522			
4. Impaired bodily functions	.345			
5. Sense of slowness			.456	
6. Poor work performance/interest	.463			
7. Poor self-care				(.271)
8. Tension, nervousness, restlessness	.666			
9. Irritability	.594			
10. Thought pressure			.511	
11. Suspiciousness/diffidence		.798		
12. Feelings of self-reference		.815		
13. Derealization			.737	
14. Changes in perception			.548	
15. Thought interference			.451	
16. Paranoid ideation		.735		
17. Hallucinations		.510		
Eigenvalues	3.41	2.43	1.90	1.67
Random eigenvalues	1.57	1.45	1.28	1.36
Explained variance (%)	20	14	11	10
Reliability estimates	.73	.84	.81	.72

Items were assigned to the factor on the basis of loading; loading <.30 were excluded, and one item only had a loading lower than this threshold (it was reported in parentheses and assigned to the factor for which it had the highest loading). Two highest loadings per each factor are set in bold

(“dysphoria” and “introversive withdrawal”). Age and sex did not influence the results (Table 3).

Latent class analysis

The 3-class was the best solution on the basis of fitting indexes, with AIC, BIC, and SSABIC all lower than in the two-class but higher than in the four-class solution; entropy of classification, too, was acceptable (Table 4).

In this solution, a baseline class was found, including patients with lower incidence of disturbed subjective experiences and paranoid autocentrism; this class included 60 patients. The class II, including 60 patients, was characterized by higher incidence of dysphoria and introversive withdrawal and lower incidence of disturbed subjective experiences and paranoid autocentrism; the other class was characterized by high incidence of psychotic-like symptoms but with dysphoria and introversive withdrawal comparable to the baseline class (class III, including 47 patients).

Figure 1 shows the ERiraos-CL item probability profiles for each class. Common features of classes I, II, and III were mostly related to interpersonal and

functional engagement (e.g., social withdrawal, shyness, reduced interest and work performance, reduced self-care) as well as emotional/affective disturbances (depressive mood, impaired bodily functions, tension/nervousness). In contrast, major differences between patients in class I and in class II compared to class III concerned paranoid-like features (e.g., suspiciousness, self-reference, persecutory ideation) and perceptual disorders (e.g., changes in perceptual vividness and hallucinatory-like experiences).

On average, patients in class II were younger than in the other classes. Compared to the baseline class I, those in class II were less likely, and those in class III were more likely to be diagnosed with FEP. There were no statistically significant differences by class on the BPRS, while those in class II were less severe on the HoNOS than those in class I (i.e., they had less associated complications such as substance abuse or self-harming behavior).

Taking into account levels of severity on the BPRS and HoNOS, GAF values were lower in the class II compared to class I, despite comparable average values because a large prevalence of less severe CHR cases in class II (Table 5).

Table 3 Association between demographic and diagnostic grouping (FEP vs CHR patients) and the multidimensional ERiraos-CL attributes (MANCOVA)

ERiraos-CL-dependent dimension	df	F	Sig.*
Corrected model, taking into account age and sex			
Dysphoria reaction	3	2.16	.95
Paranoid aut centrism	3	27.73	.0001
Introversive withdrawal	3	.70	.55
Disturbed subj. experiences	3	5.65	.001
Diagnostic grouping			
Dysphoria reaction	1	2.89	.091
Paranoid aut centrism	1	79.48	.0001
Introversive withdrawal	1	.09	.75
Disturbed subj. experiences	1	14.16	.0001
Sex			
Dysphoria reaction	1	1.76	.18
Paranoid aut centrism	1	1.31	.25
Introversive withdrawal	1	.01	.93
Disturbed subj. experiences	1	.62	.43
Age			
Dysphoria reaction	1	1.10	.29
Paranoid aut centrism	1	1.69	.19
Introversive withdrawal	1	1.91	.16
Disturbed subj. experiences	1	1.77	.18

* Statistically significant results in bold

Table 4 Fit indices for the latent class analysis of the ERiraos items

Model	AIC	BIC	SSABIC	LRT <i>p</i>	Entropy
2 classes	3,738.8	3,850.2	3,739.4	164.6 .24	.78
3 classes	3,695.2	3,863.8	3,695.9	78.8 .07	.78
4 classes	3,688.4	3,914.3	3,689.5	42.3 .80	.81
5 classes	3,675.3	3,958.4	3,676.6	44.4 .63	.84
6 classes	3,670.2	4,010.6	3,671.8	44.2 .53	.88

Discussion

This study is the first investigation of vulnerability dimensions and profiles across a wide spectrum of referrals to a dedicated early intervention program conducted in Italy. It is based on the translational attempt to reconcile the background assumptions of the CHR paradigm with real-world community-based mental health services. Its major aim is to portray the help-seeking needs for putatively prodromal and early schizophrenia phases as

naturalistically intercepted in a specialized community-based setting.

Vulnerability dimensions and classes

Despite the fact that certain heterogeneity in the referrals is expected, both the four vulnerability domains (dysphoria, paranoid aut centrism, introversive withdrawal, and disturbed subjective experience) and the three latent classes (with varying degree of proneness to schizophrenia psychosis) had considerable face validity and were clinically interpretable.

Indeed, the four components extracted from the factor analysis echoed attenuated dimensions of pre-schizophrenic disposition as conceived by the European tradition. Suffice to mention here Bleuler's iconic note on "latent schizophrenia": "Irritable, odd, moody, withdrawal ...". Almost one century ago, Bleuler explicitly acknowledged that, although rarely treated, he actually considered "latent schizophrenia" as the most frequent form of the disorder [46]. Likewise, introversive social withdrawal evokes schizoid-like interpersonal aversiveness [47–50], and observations on social inadequacies in premorbid psychotic states are disseminated all over a century of clinical and research descriptions, up to the recent notion of "social dysmetria" [51]. Also, paranoid aut centrism (which embraces unstable feelings of self-reference, paranoid suspiciousness and more articulated persecutory ideation) is a well-known psychopathological catalyser for the development of Schneiderian first rank symptoms (see [52–55]). The last component, disturbed subjective experience, encompasses non-psychotic self-experienced phenomena (such as depersonalization and thought pressure) that have been widely corroborated as indicators of schizophrenia proneness [13, 16, 31, 56–60].

Whereas the vulnerability domains provide a clinical framework to describe dimensional components of help-seeking needs (as captured by the ERiraos-CL), the identified latent classes point to three levels of schizophrenia proneness as the most parsimonious partition of the continuum of need of care in the help-seeking referrals.

The first level of risk within the real-world community-based mental health services captures behavioral severity, as exemplified by greater incidence of substance abuse or self-harming behavior in class I than in class II. People with attenuated or brief but recurring psychotic-like experiences are referred to the mental health network of care when they display consistent behavioral indicators of risk, substance abuse [61] and self-harming behavior [62] being implied in psychosis at first presentation. High levels of dysphoria and introversive withdrawal and low degrees of paranoid aut centrism and disturbed subjective experience characterize a second level of proneness to schizophrenia

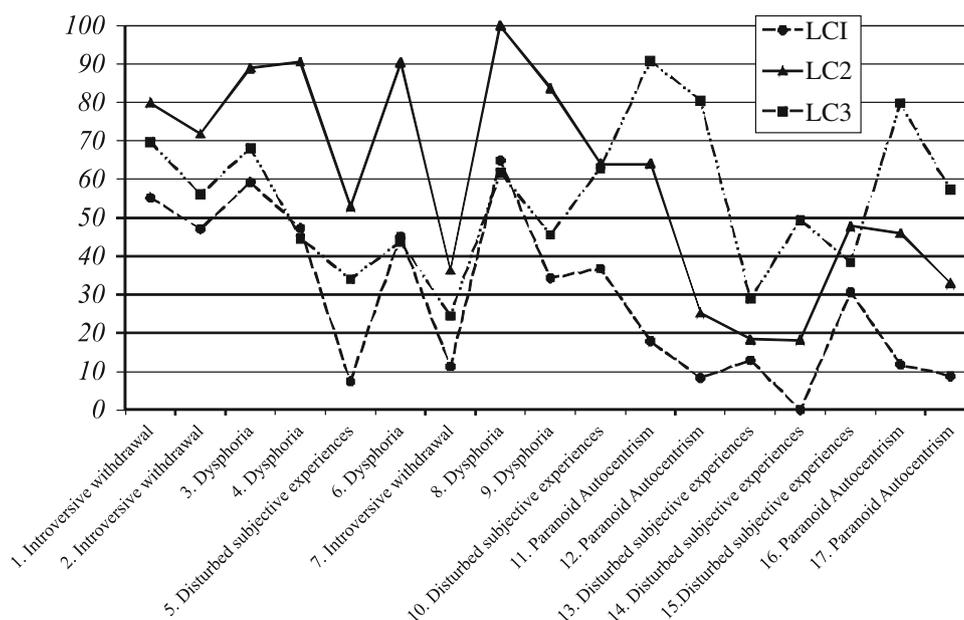


Fig. 1 Profile plots for the 3-class solution. On the Y-axis class-specific mean scores as proportions of the maximum score. On the X-axis the ERiraos 17-item symptom profile reclassified into the four dimensions: dysphoria, introversive withdrawal, disturbed subjective experience, and paranoid autocentrism (see EFA in Table 2). LC1 = low proneness to psychosis; LC2 = dysphoria/introversive withdrawal; LC3 = high proneness to psychosis. *ERiraos-CL items 1*

social withdrawal, 2 shyness, 3 depressive mood, 4 impaired bodily functions, 5 sense of slowness, 6 poor work performance/interest, 7 poor self-care, 8 tension, nervousness, restlessness, 9 irritability, 10 thought pressure, 11 suspiciousness/diffidence, 12 feelings of self-reference, 13 derealization, 14 changes in perception, 15 thought interference, 16 paranoid ideation, 17 hallucinations

psychosis, including CHR people that are less severe on a behavioral and functional ground than those in class I, but more clearly characterized within the spectrum of risk because affective and introversive symptoms.

The high proneness to schizophrenia psychosis group, on the contrary, revealed high levels on all the ERiraos-CL domains. Concretely, this means that those first-referrals with paranoid autocentrism and disturbed subjective experience on the background of (introversive) interpersonal withdrawal and reactive-tense emotional patterns (dysphoria) constitute the vulnerability group with the highest risk of being in the early phases of schizophrenia. Overall, this coheres with the results of a previous German field test [25] indicating the emergence of more characteristic ERiraos-CL patterns (such as suspiciousness, derealization, self-reference, paranoid ideation) along with the growing proximity to the onset of psychosis. Results are also congruent with the results of the ABC study [63, 64]. The relevance of introversive interpersonal withdrawal and reactive-tense emotional patterns (dysphoria) in CHR people is congruent with the high baseline prevalence of comorbid depressive and anxiety disorders in people diagnosed with at-risk mental state for psychosis [65], and the impact of affective instability and neuroticism in the transition to psychosis in people reporting psychotic-like experiences [66].

A recent 50-year follow-up of the 1947 Lundby (Sweden) cohort found that some clusters of symptoms similar to the ERiraos-CL domains that were identified in this study were strong predictors of the risk of psychosis in that cohort. [67]. In particular, the nervous-tense, paranoid-schizotypal, and tired-distracted clusters of symptoms were significantly associated with incident psychosis in the Lundby cohort study. The nervous-tense cluster is similar to the reactive-tense emotional patterns identified in the present analysis of the ERiraos-CL, the paranoid-schizotypal cluster is similar to the paranoid autocentrism domain of the ERiraos-CL, and the tired-distracted cluster reminds the sense of slowness and the thought interference that contribute to the disturbed subjective experience domain of the ERiraos-CL. The results of the Lundby cohort study give further support to the present study's findings as far as the association of the four ERiraos-CL domains in different profiles of risk is concerned.

Clinical–psychopathological implications

Despite different on definitional grounds, clinical high-risk and first-episode schizophrenia patients were similar on important psycho-behavioral features, involving affective reactivity (e.g., dysphoric irritability, tension, and

Table 5 Associations between ERiraos-CL classes with demographic factors and clinical variables in the 3-class solution (baseline Class I)

Variables	LC I	LC II	LC III
Sex (vs. females)			
Males, n (%)	34 (69.4)	42 (79.2)	37 (72.5)
O.R. (95 % CI ^a)	1	2.87 (.90–9.25)	1.75 (.65–4.74)
Age (vs. younger)			
Mean age (SD)	23.2 (3.7)	21.5 (3.4)	23.0 (3.9)
O.R. (95 % CI ^a)	1	.87 (.76–.99) ^a	1.01 (.89–1.13)
FEP (vs. CHR)			
FEP, n (%)	25 (49)	10 (18.9)	40 (81.6)
O.R. (95 % CI ^a)	1	50.4 (13.0–194) ^a	9.47 (2.97–30.1) ^a
BPRS (vs. lower)			
Mean (SD)	48.5 (12.5)	44.1 (11.1)	50.7 (16.6)
O.R. (95 % CI ^a)	1	1.01 (.96–1.07)	1.01 (.96–1.05)
HoNOS (vs. lower)			
Mean (SD)	14.0 (5.2)	12.1 (5.1)	15.4 (6.5)
O.R. (95 % CI ^a)	1	.87 (.76–.98) ^a	1.01 (.91–1.12)
GAF (vs. lower)			
Mean (SD)	48.0 (10.9)	50.4 (11.2)	47.1 (9.8)
O.R. (95 % CI ^a)	1	.94 (.88–.98) ^a	.95 (.90–1.12)

Multinomial logistic regression was carried out on less than 167 patients, since some data (HoNOS and GAF) were not available

^a Confidence intervals not including unity indicate statistical significance ($p < .05$)

nervousness) and social, inter-peer avoidance (e.g., interpersonal withdrawal, shyness).

This suggests that the combination of early social dysfunction and emotional-affective instability might be the earlier and broader feature of clinical caseness and therefore a major target for early treatment [10, 68, 69].

Pending further longitudinal studies, this could be important also for the delineation of a phenotypically broad “pluripotential risk syndrome” that indicates a need for care without attempting to define an end-stage syndrome [1, 70].

The coexistence of paranoid aut centrism and disturbed subjective experience on such “pluripotential” background (i.e., early social dysfunction and emotional-affective instability) qualified a more schizophrenia-specific stage (i.e. latent class III). Thus, paranoid aut centrism and disturbed subjective experience might be regarded as clinical features of higher specificity for the purpose of early staging.

These results, in our view, are of particular importance for the purpose of hierarchical risk enhancement, which constitutes a crucial translational strategy for the CHR paradigm. The hierarchical risk enhancement relies, first, on the self-selection of persons consulting primary health services (because of mental problems) and, then, on progressively more detailed examinations of increasing specificity. Due to its flexibility, the ERiraos-CL is an instrument that could assist the initial assessment already in first-contact sites (e.g., primary health services) to decide on the opportunity and urgency of a further detailed assessment. Our results suggest that the dimensional pattern high dysphoria–high introversive withdrawal is a plausible entry level for clinical caseness and that the co-presence of paranoid aut centrism and disturbed subjective experience indicate a more schizophrenia-specific risk. It should be borne in mind that at-risk people usually fulfill the general criteria of mental disorders [71], and the ERiraos-CL might be used to classify this population into a hierarchical profile of risk thus favoring the provision of targeted interventions. There is some evidence that the temporal variance of risk estimation by UHR criteria is broader than originally expected [72]. The ERiraos-CL might be helpful to adapt a clinical staging algorithm into a more individualized risk classification as to target interventions to the needs of a specific group.

Limitations

The above findings should be tempered by limitations associated with this study. First, for obvious pragmatic reasons, the study could not transcend the pre-existent organizational and procedural features of the Italian community-based mental health system [27, 73]. Those include high geographic variability in terms of facilities distribution, coordination standards, knowledge transfer, and informatization. This organizational variability corresponds to a wide variability across geographic areas of help-seekers with first-episode psychosis [74]. Moreover, the Italian public mental health system is mostly calibrated to provide generalist, need-based treatment particularly in support of chronic disability. Therefore, the sample is not strictly representative from the epidemiological viewpoint and a strong dispersion of candidate referrals has to be taken into account. Indeed, given the presumable incident cases of schizophrenia in the catchment area over the period 1999–2009, the number of enrolled FEP is much lower than expected. Although this is perhaps unavoidable in the real world of community MH, we could not assess its determinants retrospectively. Similarly, we do not have complete data on the subjects who were not admitted to the program (e.g., because a DUP above 2 years or absence of CHR or neurological disorder).

Second, people were included in the study when they were above a minimal severity threshold that was slightly higher than the level of severity observed in people requesting help in MH. This is because, first, those subjects who were referred by generalist MH services were already a relatively enriched sample (i.e., they had a certain clinical severity that was compatible with a suspected prodromal state) and, second, data were collected on subjects admitted to the therapeutic protocol of Programma 2000. Hence, they were further examined and included if they formally met at least one of the CHR criteria (see “[Methods](#)”).

Third, since information on psychopathological vulnerability was collected via ERiraos-CL, an instrument dedicated to screening, the degree of symptom resolution is modest compared to more articulated tools (e.g., CA-ARMS, SIPS/SOPS, SPI-A) [19], typically adopted in academic-based tertiary referral centers. We cannot exclude that the resolution power of the study was insufficient to detect more subtle zones of rarity between CHR and FEP.

Finally (partly related to the previous point), although the LCA showed the superiority of a three-class solution compared to alternative solutions with more classes (see [Table 4](#); [Fig. 1](#)), an inherent limitation of this technique is that it precludes analysis of within-class heterogeneity, including individual differences in severity. Nevertheless, the classes seem to map on meaningful psychopathological prototypes consistent with clinical practice.

Conclusion

This study investigated the profiles and latent structure of schizophrenia psychosis proneness as traceable in the initial help-seeking phase (i.e., when clinical “caseness” is intercepted by dedicated services). We found that dysphoria and introversive withdrawal were shared components of clinical caseness across all the referrals. On the contrary, paranoid aut centrism and disturbed subjective experience were related to schizophrenia psychosis proneness and therefore might be important for further closing-in and staging those CHR help-seekers with higher morbid susceptibility.

These findings are encouraging in terms of translating scientific opportunity into public health, since they provide a succinct frame for early clinical staging that—capitalizing on the flexibility of the ERiraos-CL—might improve effective community MH care in several ways. These include the personalization of care based on the vulnerability profiles, the implementation of early psychosocial interventions (e.g., targeting the shared social and affective components of clinical caseness), and the calibration of further multiple-gate assessments of increasing sophistication. In this sense, the parsimony of the current model (which defines two clinical caseness profiles of increasing schizophrenia psychosis proneness) is likely to be attractive for both research and clinical implementations of the CHR paradigm.

In sum, the study indicates that the ERiraos-CL can favor the profiling of two hierarchically related risk states in help-seeking people consulting primary health services. Whereas a combination of high dysphoria and high introversive withdrawal is a common motivation for referral, the presence of concomitant paranoid aut centrism and disturbed subjective experience may herald a more specific vulnerability to schizophrenia that ought to be taken into consideration for the purpose of rational clinical decision making.

Therefore, due to its relative simplicity, the ERiraos-CL might be fruitfully adopted both in community mental health settings (to complement the initial multimodal assessment of help-seeking youths) and in first-contact sites (to facilitate the screening of those individuals that could benefit of a further specialist referral for more comprehensive vulnerability assessment).

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Conflict of interest The authors declare no conflicts of interest.

Appendix

See [Table 6](#).

Table 6 ERiraos-Checklist synopsis

ITEM	Question	Exemplar clarification questions	Corresponding items in other instruments or relevant early detection constructs (e.g. DSM III R prodromal symptoms, DSM IV schizotypal features)
1. Social withdrawal	Do you feel that you have turned into a loner or have become less talkative?	Do you prefer to spend most of your time by yourself? Have you started to withdraw from your group of friends? Have you stopped doing things with others?	BSABS A.6.4 (diminished need for contact with others) CAARMS 5.1 (social isolation) SOPS N1 (social anhedonia or withdrawal) DSM III R prodrom (1: significant social isolation or withdrawal) DSM IV Schizotypal feature (poor rapport with others and a tendency to social withdrawal)
2. Shyness	Have you become shy and timid, and feel more and more insecure or embarrassed in contact with other people?		IRAOS 26.13 (<i>Loss of self-confidence, shyness the subject experiences himself as insecure and shy with other people</i>) DSM IV schizotypal feature (excessive social anxiety)
3. Depressive mood	Has your mood been rather depressed, sad, subdued or desperate over weeks?		BSABS A.6.1 (changes in basic mood and emotional responsiveness) BPRS 9 depressive mood CAARMS 7.2 (depression) SOPS G2 (dysphoric mood)
4. Impaired bodily functions	Has your sleeping-pattern changed? Or has your appetite or sexual interest changed?	Difficulties falling asleep, or sleeping through the night or early waking. Appetite/sexual desire significantly increased or decreased.	BSABS E1.1–E1.7 (neuro-vegetative disorders, including loss of appetite, cravings, changes in libido), E2.1–E.2.3 (sleeping problems) CAARMS 6.4 (impaired autonomic functioning) SOPS G1 (sleep disturbance), G2 (dysphoric mood: sleeping problems, poor or increased appetite)
5. Sense of slowness	Do you feel like your thinking, speaking or movements have been slowing down noticeably?		BSABS C.3.4 (psychomotor retardation), C.1.12 (retardation and retarded thought processes)
6. Poor work performance/ interest	Has your persistence, motivation or quality in your main occupation/ search for work deteriorated? Do you show less interest or commitment in your main occupation/search for work?		CAARMS 5.2 (impaired role functioning) SOPS N6 (occupational functioning) partly overlaps avolition, hypohedonia, diminished motivation, avoidance or abandonment of goal-directed activities (CAARMS 4.2, 4.3; SOPS N2)
7. Poor self-care	Do you neglect one of the following areas: Personal hygiene, clothes, manners, nutrition or health? Do you keep your home/room tidy?		CAARMS 5.3 (Disorganizing, odd, stigmatizing behavior—poor self-care) SOPS D4 (impairment in personal hygiene/social attentiveness) DSM III R prodrom (4: significant impairment or neglect of personal hygiene and body care) DSM IV schizotypal feature (neglect of external appearance—odd behavior)

Table 6 continued

ITEM	Question	Exemplar clarification questions	Corresponding items in other instruments or relevant early detection constructs (e.g. DSM III R prodromal symptoms, DSM IV schizotypal features)
8. Tension, nervousness, restlessness	Do you frequently feel nervous, restless or tense? Do you feel jumpy, edgy or do others think that you appear this way and have remarked on it?		BPRS 6 (tension) BSABS B.1.1 (Impaired tolerance to stress) CAARMS 7.8 (Impaired tolerance to stress) SOPS G2 (dysphoric mood: restlessness, agitation, tension)
9. Irritability	Are you unusually irritable or angry or do you find yourself more involved in arguments with your relatives, friends or others lately?		BSABS B.2.4 (increased reactivity and irritability) CAARMS 7.4 (Mood swings/lability) SOPS G2 (dysphoric mood: irritability, hostility, rage)
10. Thought pressure	Does it happen that different thoughts are getting mixed up and whirling in your mind?	Do you find it very difficult to control, structure or stop your thoughts?	BSABS C.1.3 (pressing and racing thoughts: numerous thoughts appear in quick succession and impose themselves without the subject being able to control this)
11. Suspiciousness, diffidence	Do you lately often have the impression that other people are trying to take advantage of you or deceive you?		BPRS 11 (suspiciousness) PDI 21 (13: worrying about one's partner's faithfulness) CAARMS 1.2 (Non-bizarre ideas: suspiciousness, persecutory ideas) SOPS P2 (suspiciousness/persecutory ideas: a) Excessive concern about the motivations of others; distrustful) DSM IV schizotypal feature (suspiciousness, distrust)
12. Feelings of self-reference	Do you increasingly feel that certain everyday events or actions of other people are exclusively addressed to you, even if you know at the same time that this is unlikely?	Do you have the feeling that other people talk or laugh about you? Or do you receive messages through the radio, TV, newspapers containing some special meaning for you or hints that they are exclusively addressed to you?	BSABS C.1.17 ('subject-centrism': unstable ideas of reference) CAARMS 1.1 (unusual thought content: ideas of reference) SOPS P1 (unusual thought content/delusional ideas: (b) ideas of reference) DSM IV schizotypal feature (ideas of reference)
13. Derealization	Do your usual surroundings occasionally appear to be transformed, unreal or strange?	Do landscapes, animals or people occasionally appear to be particularly magnificent, impressive, moving, threatening or unreal?	BSABS C.2.11 (derealisation) CAARMS 7.7 (dissociative symptoms: derealisation) SOPS N4 (Experience of emotions and self: feeling unreal, disconnected from the world) DSM IV schizotypal feature (unusual perceptual experiences)

Table 6 continued

ITEM	Question	Exemplar clarification questions	Corresponding items in other instruments or relevant early detection constructs (e.g. DSM III R prodromal symptoms, DSM IV schizotypal features)
14. Changes in perception	At any time in your life, did you ever experience that people or things in your environment appeared to be changed?	Did you experience that your hearing or vision was outstandingly intense or supernaturally clear? Or sometimes people and things seem changed with regard to their color, shape or magnitude? Or did you perceive things particularly intensive or glaring?	BSABS C.2.2 (sensitivity to light), C.2.4 (sensitivity to noises) CAARMS 1.3 (Perceptual abnormalities: heightened or dulled perceptions) SOPS P4 (perceptual abnormalities/hallucinations: (a) unusual perceptual experiences: heightened or dulled perceptions) DSM IV schizotypal feature (unusual perceptual experiences)
15. Thought interference	At any time in your life, did you sometimes experience that your train of thoughts was suddenly interrupted or disturbed by other thoughts?		BSABS C 1.1 (thought interference), C1.4 (thought block)
16. Paranoid ideation	At any time in your life sometimes you felt observed, persecuted or threatened by something or somebody?		BPRS 11 (suspiciousness) PDI 21 (4: being persecuted in some way) PDI 21 (5: conspiracy against you) SOPS P2 (suspiciousness/persecutory ideas: (b) suspiciousness or paranoid thinking) DSM IV schizotypal feature (Ideas of reference, suspiciousness)
17. Hallucinations	At any time in your life sometimes you could see, hear, smell or taste things that other people could not sense. You couldn't explain these experiences in terms of natural causes?	Did you sometimes hear noises or voices while on your own?	CAARMS 1.3 (Perceptual abnormalities: visual, auditory, olfactory, gustatory, tactile, somatic hallucinations) SOPS P4 (perceptual abnormalities/hallucinations: (b) pseudo-hallucinations; (c) occasional frank hallucinations) DSM IV schizotypal feature (occasional transient quasi-psychotic episodes with intense illusions, auditory or other hallucinations)

Acronyms: Brief Psychiatric Rating Scale (BPRS), Bonner Skala für die Beurteilung von Basissymptomen (BSABS), Comprehensive Assessment of At-Risk Mental States (CAARMS), Interview for the Retrospective Assessment of the Onset of Schizophrenia (IRAOS), Peters Delusional Inventory (PDI-21), Scale of Prodromal Symptoms (SOPS)

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