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Development of a stage-dependent prognostic model to predict psychosis in ultra-high risk patients seeking treatment for co-morbid psychiatric disorders

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Abstract

Background

Current ultra-high-risk (UHR) criteria appear insufficient to predict imminent onset of first-episode psychosis, as a meta-analysis showed that about 20% of patients have a psychotic outcome after 2 years. Therefore, we aimed to develop a stage-dependent predictive model in UHR individuals who were seeking help for co-morbid disorders.

Method

Baseline data on symptomatology, and environmental and psychological factors of 185 UHR patients (aged 14-35 years) participating in the Dutch Early Detection and Intervention Evaluation study were analyzed with Cox proportional hazard analyses.

Results

At 18 months, the overall transition rate was 17.3%. The final predictor model included five variables: observed blunted affect (hazard ratio (HR) 3.39, 95% confidence interval (CI) 1.56-7.35, $p < 0.001$), subjective complaints of impaired motor function (HR 5.88, 95% CI 1.21-6.10, $p = 0.02$), beliefs about social marginalization (HR 2.76, 95% CI 1.14-6.72, $p = 0.03$), decline in social functioning (HR 1.10, 95% CI 1.01-1.17, $p = 0.03$), and distress associated with suspiciousness (HR 1.02, 95% CI 1.00-1.03, $p = 0.01$). The positive predictive value of the model was 80.0%. The resulting prognostic index stratified the general risk into three risk classes with significantly different survival curves. In the highest risk class, transition to psychosis emerged on average $\geqslant$8 months earlier than in the lowest risk class.

Conclusions

Predicting a first-episode psychosis in help-seeking UHR patients was improved using a stage-dependent prognostic model including negative psychotic symptoms (observed flattened affect, subjective impaired motor functioning), impaired social functioning and distress associated with suspiciousness. Treatment intensity may be stratified and personalized using the risk stratification.

Introduction

Current ultra-high-risk (UHR) criteria, emphasizing recent onset or worsening of subthreshold psychotic symptoms (1–4), appear to be insufficient in predicting imminent onset of first-episode psychosis, as about 20% show a psychotic outcome at 2 years follow-up (5). Therefore, the challenge is to develop a prognostic model to more precisely identify those individuals most likely to make a transition from UHR to a first-episode psychosis. In this context it should also be noted that the UHR stage could be divided into substages, in which people have progressed to an even more elevated stage of an imminent risk of a first psychosis. In each of these stages a different set of prognostically relevant factors could play a role. In the present study we aimed to increase predictive accuracy, while also taking into account the specific UHR stage. This stage-dependent prognostic modeling approach is relevant, because it can help improve the continuity of well-tailored (personalized) proactive care for individuals with a poor prognosis.

The PACE400 Study (6) and two large multi-center studies aimed to identify specific predictors of transition to psychosis. The PACE400 Study included a cohort of UHR patients recruited to participate in research studies between 1993 and 2006. A two-factor prediction rule was obtained: poor functioning at baseline, and the duration of symptoms before clinic entry. Patients at UHR with either one or both of these factors had a chance of 39%, 52%, or 72% of developing psychosis within, respectively, 1, 3 or 5 years. However, similar to other models attempting to narrow the criteria (7), the loss of sensitivity was unfavorably high (8). The North American Prodrome Longitudinal Study (NAPLS) (9), found five baseline variables contributing uniquely to the prediction of psychosis: a genetic risk for schizophrenia with recent functional decline, higher levels of unusual thought content, higher levels of paranoia, greater social impairment, and history of any drug abuse. In their population, algorithms combining two or three of these variables maximized the positive predictive value (PPV) to 74–81% compared with 35% for the UHR criteria alone. However, similar to other models (7) and the PACE400 Study (6), the loss of sensitivity was also high (8).

The European Prediction of Psychosis Study (EPOS) (7), developed a six-variable prediction model including the following baseline features: overall severity of positive symptoms, bizarre thinking, sleep disturbance, schizotypal personality disorder, loss of functioning in the past year, and years of education. Although the model produced an excellent positive likelihood ratio (+LR) of 19.9, again, there was considerable loss of sensitivity (7). Using the Cox equation to calculate a prognostic score for each participant counteracted this disadvantage. Furthermore, this enabled us to introduce a prognostic index by stratifying the score and, thus, the general risk of the sample, into different risk classes, allowing both more individualized risk estimation and preservation of the sensitivity of the inclusion criteria.

However, in the above-mentioned studies, the UHR criteria used differed slightly. The PACE400 study used the Comprehensive Assessment of At Risk Mental State (CAARMS) and the sample was recruited before the introduction of the social decline criterion (4). The NAPLS used the Structured Interview for Prodromal Syndromes (SIPS), also without a social decline criterion. The EPOS used the SIPS and basic symptom-based criterion for cognitive disturbances (COGDIS). All three studies recruited both cases and persons not yet classified as a case. To restrict the UHR group to a sample at imminent risk of transitioning to a first episode of psychosis would be more relevant from a clinical point of view. Such a restriction would serve to recruit patients with stage 1b as described by McGorry et al. (2006) (10) in their staging model for psychotic disorders. This latter group is characterized by psychotic-like experiences with distress, help-seeking for co-morbid disorders, and reduced functioning. This is the stage where 'caseness' demands therapy for persons at imminent risk of psychosis (10,11).

Therefore, in the present study we aimed to develop a stage 1b-dependent prognostic model by recruiting a sample of young people aged ⩽35 years who are seeking help in mental health services for an Axis-1 or Axis-2 DSM-IV disorder and who also fulfil the criteria of the CAARMS, including low functioning.

Method

Design and recruitment

The EDIE-NL study is a randomized controlled trial (RCT) in which add-on cognitive behavior therapy (CBT) was compared with treatment as usual (TAU) alone (12). Participants were recruited by screening or referral at four treatment centers between February 2008 and February 2010. Inclusion criteria of the EDIE-NL trial were composed of the UHR criteria, assessed by the CAARMS (3,4): 'Familial Risk', Attenuated Psychotic Symptoms, Brief Limited Intermittent Psychotic Symptoms (BLIPS), each accompanied by a score of ⩽50 on the Social and Occupational Functioning Assessment Scale (SOFAS) (13), and/or a reduction of 30% on this scale for at least 1 month in the past year. Exclusion criteria were: a psychotic episode lasting ⩾1 week, i.e. fulfilling the DSM-IV criteria of a brief psychotic episode within a time period of ⩾7 days assessed with the Schedules for Clinical Assessment in Neuropsychiatry (SCAN 2.1) (14); current/previous use of antipsychotic medication with a cumulative dose of ⩾15 mg haloperidol equivalents; severe learning impairment, and/or insufficient competence in the Dutch language. Details of inclusion and exclusion criteria are described elsewhere (12,15).

After providing informed consent, 201 individuals agreed to participate. Five participants were removed from the analyses because, retrospectively, two turned out to be already

psychotic at inclusion and three disclosed a history of psychosis during the trial. Of the remaining 196 patients enrolled in the study, 185 (88 CBT **v**. 97 TAU) had at least one follow-up clinical evaluation and comprised the final sample. The study was approved by the local Medical Ethics Committee for mental health service research and registered at Current Controlled Trials (ISRCTN21353122).

Interventions

Both arms of the study were treated with TAU provided for non-psychotic DSM-disorders for which they were seeking treatment. TAU was given according to the evidence-based clinical guidelines for non-psychotic Axis-1 or Axis-2 disorders. The experimental group received TAU plus individual CBT aimed at preventing the onset of a first psychosis. The intervention consisted of CBT enriched with education on dopamine supersensitivity, the effects of dopaminergic supersensitivity on perception and reasoning, and a cognitive bias awareness training (16).

Clinical assessments and follow-up

The present analyses used data assessed by the CAARMS (3,4), including the SOFAS (13), the Beck Depression Inventory – II (BDI-II) (17), the Calgary Depression Scale (CDS) (18), the Personal Beliefs about Illness Questionnaire (PBIQ-R) (19), the Social Interaction Anxiety Scale (SIAS) (20), the Manchester Short Assessment of Quality of Life (MANSA) (21), the Composite International Diagnostic Interview (CIDI; alcohol and drug section) (22)], and socio-demographic data including years of education and ethnicity (12). The seven CAARMS subscales (Positive, Negative, Cognitive Symptoms, Emotional Disturbances, Behavioral Change, Motor/Physical Change, and General Psychopathology) are rated on a 7-point intensity and frequency scale (0–6). The four positive symptoms each include a distress score on a 0–100 scale (Supplementary Table S1). The developer of the CAARMS criteria (A. Yung) extensively trained the investigators. Pairwise inter-rater concordance for CAARMS was 81%. Follow-up CAARMS assessments took place at 2, 4, 6, 9, 12, 15 and 18 months post-baseline. Transition to psychosis was operationalized as a continuation of full-blown psychotic symptoms for $\geqslant$7 days according to the CAARMS. The Dutch version of the SCAN (14) was used to assess past/current psychotic disorders with a view to the exclusion criteria, as well as to establish a psychotic diagnosis in case of transition.

Statistical analysis

Statistical analyses were performed using SPSS version 21.0 (IBM Corp., USA). Comparisons of general characteristics were analyzed with the Mann-Whitney **U** test, **t** tests and $\chi 2$ tests. To develop the prediction model, Cox proportional hazard analyses were used that estimate the effect of covariates on time to transition. In line with the analyses described by

Ruhrmann et al. (2010), Nieman et al. (2014) and Cornblatt et al. (2015) (7,23,24), potential model predictors were selected in a sequential procedure (25). First, univariate Cox regression analyses were performed and predictors that were significant at a liberal level ($p < 0.20$) were analyzed further. Second, backward multivariate Cox regression analyses were performed within each domain ($p < 0.15$). Third, retained covariates were entered into domain-specific multivariate backward Cox regressions ($p < 0.05$). Fourth, all variables with a significant test result in the previous univariate or multivariate analysis were added one-by-one to the preliminary model and kept in the model if they remained significant. Finally, the remaining covariates from steps 3 and 4 were analyzed together forward and backward to exclude effects of blocking ($p < 0.05$), restricting the maximum number of predictors entering the final model to a 1:5 ratio of number of predictors to events, i.e. to six predictors (26). Wald $\chi 2$ was used to test the significance of individual variables in the model. Recruitment strategy (referral, screening or mixed) was entered as a strata variable in all analyses. According to the state-of-the-art manual of Hosmer and Lemeshow (25), the CBT intervention was introduced as a possible confounding factor. Developing the model on the TAU sample and testing it on the CBT sample was not possible due to a lack of sufficient power. To circumvent the risk of an overfitted model, and to check the internal validity of the final prediction model, a bootstrap method was employed (27,28). The approach for risk stratification is described elsewhere (7,23). Following this approach, the resulting Cox regression equation was used to calculate individual prognostic scores. A prognostic index (PI) was generated to differentiate risk classes to aid in predicting the prognosis of UHR patients (7). PIs were calculated for the total sample. The obtained PI was applied to the CBT and TAU subsample to analyze how the PI ranges work with or without CBT treatment. Subsequently, a log-rank test was performed to compare the risk classes on time to transition and hazard ratio (HR) ($p < 0.05$). Finally, the individual prognostic scores were entered into a binary logistic regression analysis to calculate sensitivity, specificity, +LR and −LR, and the PPVs and negative predictive values (NPVs) of the Cox model and model discrimination was assessed with the area under the curve (AUC).

Results

Baseline data and tests of attrition bias

Of the 185 subjects, 18 (9.7%) were lost to the 18-month follow-up. Patients with known outcome showed no significant difference ($p < 0.05$) compared with those lost to follow-up in terms of socio-demographic characteristics and clinical characteristics (Tables 1 and 2).

Table 1. Socio-demographic sample characteristics with known and unknown CAARMS outcome of the Dutch EDIE-NL study

Characteristics	Total sample (n=185)	Known outcome[a] (n=167)	Unknown outcome[b] (n=18)	Statistic[c]	*p*-value
Age, mean ± SD, years	22.73± 5.5	22.8 ± 5.5	21.7 ± 4.9	U=1314.0	0.38
Female sex (%)	95 (51.4)	85 (50.9)	10 (55.6)	$\chi 2(1)=0.141$	0.70
Education, including university, mean ± SD, years[d]	12.7 ± 2.8	12.6 ± 2.8	13.2 ± 2.9	t(183)=-.808	0.42
Current work situation, n (%)				$\chi 2(1)=0.4$	0.52
Paid job/unpaid job/school	143 (77.3)	128 (76.6)	15 (83.3)		
Unemployed/otherwise	42 (22.7)	39 (23.4)	3 (16.7)		
Current marital status and living situation, n (%)				$\chi 2(1)=0.4$	0.55
Single/divorced	144 (77.8)	131 (78.4)	13 (72.2)		
Married/living Together	41 (22.2)	36 (21.6)	5 (27.8)		
Surrounding address density (%)[e]				$\chi 2(1)=0.5$	0.48
Urban (>2.500)	107 (57.8)	98 (58.7)	9 (50.0)		
Rural (<2.500)	78 (42.2)	69 (41.3)	9 (11.5)		
Ethnicity, n (%)[f]				$\chi 2(1)=0.5$	0.48
Dutch	107 (57.8)	98 (58.7)	9 (50.0)		
Moroccan/Turkish/ Surinamese/Other	78 (42.2)	69 (41.3)	9 (50.0)		

Note: CAARMS, Comprehensive Assessment of At-Risk Mental States; EDIE, Early Detection and Intervention Evaluation; SD, Standard deviation. [a] All persons making a transition to psychosis during the 18-month follow-up or completing it. [b] Persons with an observation time ≤ 18 months and unknown CAARMS outcomes. [c] Continuous variables were compared using the Mann-Whitney U test; categorical variables were compared using the χ2 or Fisher exact test. [d] To keep all β coefficients positive, years of education have been inverted by rank transformation in a scale from 1-17 (higher number indicates fewer years of education, e.g. 17=8 years of education, 16=9 years of education). [e] Average number of addresses within a 1-km radius as a (Dutch) measure of the degree of urbanisation (http://www.cbs.nl): 2,500 addresses or more per square km =extremely urbanised. [f] We used the classification of ethnicity as defined by the Dutch Bureau of Statistics (http://www.cbs.nl).

Table 2. Clinical Sample Characteristics in patients with known and unknown CAARMS outcome

Characteristics	Baseline, mean ± SD				
	Total sample (n=185)	Known outcome[a] (n=167)	Unknown outcome[b] (n=18)	Test statistic[c]	p-value[d]
CAARMS sum scores					
Total	52.7 ± 15.9	52.7 ± 15.7	52.6 ± 18.7	t(183)=0.1	0.98
Positive symptoms intensity (0-24)[e]	10.3 ± 2.8	10.3 ± 2.7	10.3 ± 3.5	t(183)=-0.1	0.95
Negative symptoms intensity (0-18)[e]	7.1 ± 3.5	7.1 ± 3.5	6.8 ± 3.5	t(183)=0.3	0.74
Cognitive change intensity (0-12)[e]	3.4 ± 1.9	3.4 ± 1.9	3.4 ± 1.8	t(183)=-0.2	0.84
Emotional disturbance (0-18)[e]	3.6 ± 2.5	3.6 ± 2.6	3.6 ± 2.4	t(183)=-0.0	1.00
Behavioral change (0-12)[e,f]	3.0 ± 2.0	3.07 ± 2.1	2.61 ± 1.6	t(183)=0.9	0.36
Motor/physical Change (0-24)[e]	3.9 ± 3.4	3.87 ± 3.4	4.56 ± 3.2	t(183)=-0.8	0.42
General psycho-pathology (0-48)[e]	15.1 ± 6.1	15.15 ± 6.2	14.65 ± 5.1	t(182)=0.3	0.75
CIDI any drug abuse and/or dependence (%)	57 (30.8)	54 (32.3)	3 (16.7)	$\chi2(1)=1.9$	0.17
BDI-II Depression sum score (0-63)	21.9 ± 12.2	21.8 ± 11.9	22.5 ± 15.4	t(183)=-0.2	0.83
CDS Depression sum score	6.1 ± 4.6	6.0 ± 4.6	6.4 ± 5.0	t(183)=-0.3	0.76
SIAS Anxiety sum score (0-76)	31.8 ± 16.8	32.0 ± 16.2	29.4 ± 21.5	t(183)=0.6	0.54
PBIQ-R Dysfunctional beliefs	74.1 ± 16.4	74.0 ± 15.9	75.9 ± 21.4	t(183)=-0.5	0.64
MANSA Quality of Life (12-84)[g]	34.4 ± 12.0	34.5 ± 11.8	33.8 ± 13.6	t(183)=0.2	0.82
1st- or 2nd- or 3rd-degree relative with psychosis (%)	63 (34.1)	57 (34.1)	6 (33.3)	$\chi2(1)=0.1$	0.95
First- or second-degree relative with psychosis (%)	47 (25.4)	42 (25.1)	5 (27.8)	$\chi2(1)=0.1$	0.81
DSM-IV diagnosis (%)				$\chi2(11)=14.6$	0.20
Anxiety disorders	51 (27.60)	45 (26.9)	6 (33.3)		
Depression	48 (25.9)	43 (25.7)	5 (27.8)		
Mixed anxiety and depression	10 (5.4)	9 (5.4)	1 (5.6)		
Personality disorders	15 (8.1)	15 (9.0)	-		
Attention deficit hyperactivity disorder	13 (7.0)	11 (6.6)	2 (11.1)		
Drug abuse or dependence	9 (4.9)	9 (5.4)	-		

Table 2. Clinical Sample Characteristics in patients with known and unknown CAARMS outcome - *continued*

Characteristics	Baseline, mean ± SD				
	Total sample (n=185)	Known outcome[a] (n=167)	Unknown outcome[b] (n=18)	Test statistic[c]	p-value[d]
DSM-IV diagnosis (%) (continued)				χ2(11)=14.6	0.20
Eating disorder	9 (4.9)	8 (4.8)	1 (5.6)		
Posttraumatic stress disorder	8 (4.3)	8 (4.8)	-		
Oppositional defiant disorder	5 (2.7)	5 (3.0)	-		
Asperger syndrome	5 (2.7)	5 (3.0)	-		
Relationship problems	5 (2.7)	5 (3.0)	-		
Other problems	7 (3.8)	4 (2.4)	3 (16.7)		
Condition, No. (%)				χ2(1)=0.5	0.48
TAU	88 (47.6)	78 (46.7)	10 (55.6)		
TAU plus add-on CBT[h]	97 (52.4)	89 (53.3)	8 (44.4)		
SOFAS score at inclusion (0-100), mean ± SD[i]	54.1 ± 5.00	54.0 ± 5.0	54.9 ± 5.12	t(183)=-0.8	0.46
Recruitment strategy, No. (%)				χ2(2)=5.7	0.06
Screening	85 (45.9)	80 (47.9)	5 (27.8)		
Referral	35 (18.9)	28 (16.8)	7 (38.9)		
Mixed	65 (35.1)	59 (35.3)	6 (33.3)		
CAARMS entry route, No. (%)				χ2(1)=0.9	0.35
Genetic risk only	36 (19.5)	31 (18.6)	5 (27.8)		
APS only	149 (80.5)	136 (81.4)	13 (72.2)		
Bullied in past, No. (yes, %)	105 (56.8)	100 (59.9)	5 (27.8)	χ2(1)=6.8	0.01
Degree of bullying, No. (yes, %)				χ2(2)=6.9	0.03
Mild	32 (17.3)	30 (18.0)	2 (11.1)		
Moderate or serious	73 (39.5)	70 (41.9)	3 (16.7)		

Note: APS, Attenuated Psychotic Symptoms; BDI, Beck Depression Inventory; BLIPS, Brief Limited and Intermittent Psychotic Symptoms; CAARMS, Comprehensive Assessment of At-Risk Mental States; CBT, Cognitive Behavior Therapy; CDS, Calgary Depression Scales; CIDI, Composite International Diagnostic Interview; MANSA, Manchester Short assessment of Quality of Life; PBIQ-R, Personal Beliefs about Illness Questionnaire-Revised; SIAS, Social Interaction Anxiety Scale; SOFAS, Social and Occupational Functioning Assessment Scale; TAU, treatment-as-usual; UHR, ultra-high risk. [a] All persons transitioning to psychosis during the 18-month follow-up or completing it. [b] Persons with an observation time ≤ 18 months and unknown outcomes. [c] Continuous variables were compared using the t-test; categorical variables were compared using the χ2 or >>

<< Fisher exact test. [d] Significant at a Bonferroni-adjusted a level <0.0016. [e] The numbers between the brack-etsindicate the score range. For example, the positive symptoms scale is comprised of four subscales (unusual thought content, non-bizarre ideas, perceptual abnormalities, and disorganized speech), each with a global rating scale ranging from 0-6. Therefore, on the positive symptoms scale the minimum score that can be obtained is 0 and the maximum is 24. [f] CAARMS symptoms: 'social isolation' and 'impaired role function' were not taken into account for the analyses because of their overlap with the SOFAS. [g] To keep all β coefficients positive, MANSA scores were inverted by subtracting 84 (higher score indicates a lower level, e.g., an original score of 20 equals 64). [h] TAU+CBTuhr=treatment-as-usual plus cognitive behavioral therapy for UHR (exper-imental condition) [i]To keep all β coefficients positive, SOFAS scores were inverted by subtracting 100 (higher score indicates a lower level, e.g., an original score of 40 equals 60).

Transition to psychosis

In the present study, we analyzed 185 subjects with at least one follow-up clinical evaluation. The mean observation period was 451.5 (standard error (s.e.) = 11.8, median 540.0) days. During the 18 months follow-up, 32 subjects made a transition to psychosis. The instanta-neous incidence rate (iIR), i.e. the HR, of transition to psychosis after 6, 12 and 18 months was 0.054, 0.130 and 0.173, respectively. The mean time to transition from baseline examination was 491.6 (s.e. = 10.2, 95% confidence interval (CI) = 471.67–511.51) days.

Prediction model

The final predictor model, adjusting for recruiting strategy, included five variables: CAARMS-Observed intensity of blunted affect (any score >2), CAARMS-Intensity of subjec-tive complaints of impaired motor function (any score >2), PBIQ-R subjectively perceived social marginalization score (any score > 15), declined social functioning (as assessed with the SOFAS), and distress associated with non-bizarre ideas. The resulting equation was (1.220 x CAARMS-Observed intensity of blunted affect ⩾3) + (0.999 x CAARMS-Intensity of subjective complaints of impaired motor function ⩾3) + (1.017 x PBIQ-R social marginal-ization score ⩾16) + (0.084 x (100 – SOFAS score –54.0486)) + (0.017 x (CAARMS-distress associated with non-bizarre ideas-54.87)). The SOFAS score was inverted by subtracting 100. The continuous covariates were centered around the mean, to make survival functions rela-tive to the mean of continuous variables rather than relative to the minimum (25). A syntax for the regression formula can be obtained from the first author. The 3.388 HR emerging for the variable CAARMS-Observed intensity of blunted affect score of ⩾3 was the highest (Table 3), indicating that patients with a total subscale score of 3–6 transitioned to psychosis at a rate 3.388 times higher than patients with a lower score.

The small number of transitions to psychosis precluded splitting to generate a developing and a validation sample. Therefore, we applied a bootstrap procedure generating 1000

samples for testing the robustness of the developed prediction model. The bootstrapped results are: CAARMS-Observed blunted affect ⩾3, β = 1.22 (s.e. = 0.43, 95% CI 0.42–2.10, **p** = 0.001); CAARMS-Subjective complaints of impaired motor function intensity ⩾3, β = 0.999 (s.e. = 0.42, 95% CI 0.21–1.88, **p** = 0.01); PBIQ-R social marginalization, β = 1.017 (s.e. = 0.46, 95% CI 0.13–1.95, **p** = 0.01); SOFAS, β = 0.08 (s.e. = 0.04, 95% CI 0.02–0.17, **p** = 0.02); and CAARMS-distress associated with non-bizarre ideas β = 0.02 (s.e. = 0.01, 95% CI 0.01–0.04, **p** = 0.01). If the CI fails to include 0, then the **p** value is deemed to be ⩽0.05 and the effect is said to be significant (27). Therefore, it can be concluded that all predictors in the Cox model were still significant and that our model had a good internal validity.

Effect of add-on CBT treatment

According to the state-of-the-art manual (25), the effect of CBT treatment (**n** = 88, 47.6%) on the predictor model was tested by adding the treatment variable in a second block to the model, resulting in β = 0.520 (s.e. = 0.42) and Wald = 1.57 with HR 1.68 (95% CI 0.75–3.80). All five variables of the initial predictor set (Table 3) continued to make a significant contribution to the equation, whereas CBT no longer made a significant contribution to the model in the final multivariate analysis without blocking (**p** = 0.21).

Table 3. Cox Proportional Hazard Model

Predictor Domain	Predictor Variable	β	SE	Wald	HR (95% CI)	p- value
Emotional disturbance, CAARMS	Observed blunted affect intensity ≥3 on CAARMS	1.220	0.395	9.527	3.388 (1.561 – 7.354)	0.002
Motor/ Physical Changes, CAARMS	Subjective complaints of impaired motor function intensity ≥3 on CAARMS	0.999	0.412	5.883	2.716 (1.211 – 6.088)	0.015
Burden	Social marginalization, cut-off ≥16 on PBIQ-R	1.017	0.453	5.028	2.764 (1.137 – 6.723)	0.025
SOFAS score	SOFAS score[a]	0.084	0.038	4.970	1.088 (1.010 – 1.172)	0.026
Positive symptoms, CAARMS	Distress on CAARMS Non-bizarre ideas distress	0.017	0.007	6.055	1.017 (1.004 – 1.032)	0.014

Note: CAARMS, Comprehensive Assessment of At-Risk Mental States; CI, confidence interval; HR, hazard ratio; PBIQ-R, personal beliefs about illness questionnaire; SOFAS, Social and Occupational Functioning Assessment Scale. [a] To keep all β coefficients positive, SOFAS scores have been inverted by subtracting 100 (higher score indicates lower level, e.g., an original score of 40 equals 60).

Table 4. Risk classes of the Prognostic Index (n=185)

Characteristic	I <-0.09		
Prognostic score [a]	Total sample	CBT sample	TAU sample
No. of patients	56 (30.3%)	26	30
No. of transitions	2 (3.6%)	1	1
Estimated time (days) to transition, mean (SE), 95% CI	539.9 (11.4), CI 517.6 – 562.2	548.0 (0.0), CI 548.0 – 548.0	533.4 (14.4), CI 505.2 – 561.6
iIR of transition to psychosis			
At month 6	0.019	N/A	0.034
At month 12	0.019	N/A	0.034
At month 18	0.060	0.074	0.034

Note: CI, confidence interval; iIR, instantaneous incidence rate; No., number; SE, standard error. [a]The prognostic score is calculated as (1.220xCAARMS-Observed intensity of blunted affect≥3) + (0.999xCAARMS-Intensity >>

Prognostic index

Individual prognostic scores were calculated by applying the final Cox model to each subject. Based on the resulting prognostic score, a PI with three risk classes could be generated (Table 4).

Fig. 1 shows the corresponding Kaplan–Meier survival curves for the three risk classes calculated on the total sample. The 18-month HRs for classes I, II and III were 0.060, 0.176, and 1.569, respectively. With regard to the survival curves, class I differed significantly from class III ($\chi2(1) = 57.26$, $p < 0.001$). Furthermore, class I differed significantly from class II ($\chi2(1) = 4.21$, $p < 0.04$) and class II from class III ($\chi2(1) = 52.00$, $p < 0.001$). The mean time to transition in class III differed from class II by 215.5 days and from class I by 248.3 days, with a totally distinct 95% CI. Applying the prognostic index to the CBT and TAU subsamples separately produced comparable HRs for risk class I and II compared to the HR of the whole sample. The HR for risk class III of the TAU subsample was comparable to the HR of the whole sample (Table 4). Furthermore, the survival curves are distinct in both subsamples.

Prognostic accuracy measures

As prognostic accuracy measures cannot be analyzed with censored data, our calculations had to rely on the subsample with a known state of transition at 18 months follow-up (**n** = 167; 90.3%). Of note, there was no difference in the prognostic scores between the subsamples

II -0.09 to 1.84			III >1.84		
Total sample	CBT sample	TAU sample	Total sample	CBT sample	TAU sample
106 (57.3%)	55	51	23 (12.4%)	7	16
14 (13.2%)	7	7	16 (69.5%)	2	14
507.1 (12.0), CI 483.7 – 530.6	513.7 (15.8), CI 482.8 – 544.5	500.4 (17.9), CI 465.3 – 535.5	291.6 (35.1), CI 222.8 – 360.4	422.4 (75.2), CI 275.0 – 569.8	253.6 (29.6), CI 195.5 – 311.7
0.040	0.039	0.041	0.245	0.336	0.208
0.105	0.080	0.132	1.007	0.336	1.310
0.176	0.193	0.158	1.569	0.336	2.692

<< of subjective complaints of impaired motor function≥3) + (1.017xPBIQ-R social marginalization score≥16) + (0.084x(100-SOFAS score-54.0486)) + (0.017x(CAARMS-distress associated with non-bizarre ideas-54.87)).

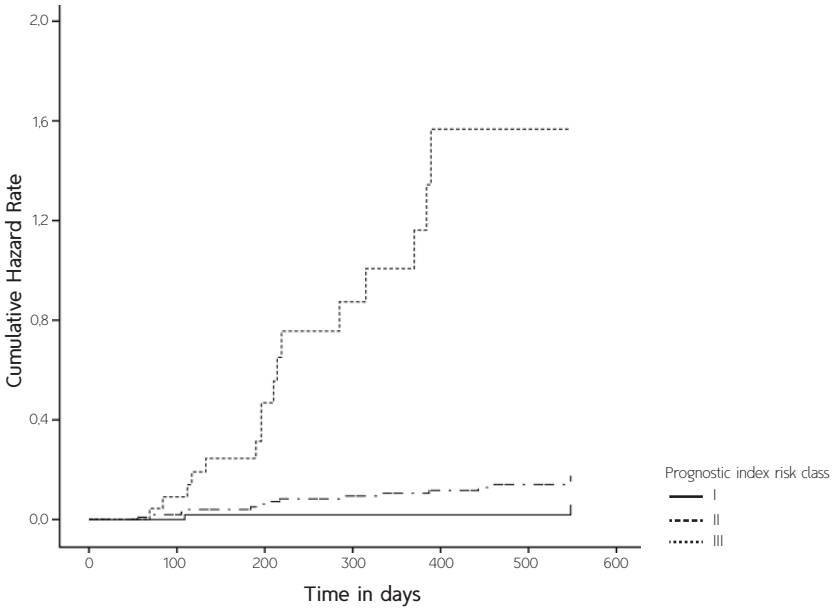

Figure 1. Kaplan-Meier survival analysis for risk classes of prognostic index (n=187);
18-month hazard rate. class I = 0.060, class II = 0.176, and class III = 1.569.

with known or unknown state of transition (**U** = 1314.50, **p** = 0.38). In total 32 (19.2%, CBT 10 **v.** TAU 22) of the 167 patients (CBT 78 **v.** TAU 89) made a transition to psychosis within 18 months. In risk class III, 80.0% (CBT 2/78 = 2.6% **v.** TAU 14/89 = 15.7%) transitioned to psychosis within the same time-frame compared to 14.6% (CBT 7/78 = 9.0% **v.** TAU 7/89 = 7.9%) in risk class II and 3.9% (CBT 1/78 = 1.3% **v.** TAU 1/89 = 1.1%) in risk class I.
Entering the prognostic scores of the whole sample in the binary logistic regression with the default probability threshold of 0.50, sensitivity was 0.38; specificity was 0.98, with a PPV = 0.80 and a NPV = 0.87. The +LR was 19.0 and the −LR was 0.63. The overall accuracy of the model was 86.2%. The AUC of the EDIE prediction model was 0.81 (s.e. = 4.4, 95% CI 71.90–89.20, **p** < 0.001).

Discussion

Our results indicate that a predictor model consisting of five baseline variables (observed blunted affect, subjective complaints of impaired motor function, subjectively experienced social marginalization, decline in social functioning, and distress associated with non-bizarre ideas) can significantly improve accuracy in predicting future psychosis in a help-seeking UHR stage-1b sample of patients with low functioning. From a clinical viewpoint, this stage is most important because the 'caseness' demands therapy for persons at imminent risk of psychosis (10,11). The AUC of the EDIE prediction model showed an excellent ability to discriminate between transition and non-transition. The +LR of 16.9 indicates that a positive classification makes it 17 times more likely to develop a psychosis than a negative test. The PPV of 80.0% also indicates that the model, which is comparable to that used in other studies (7,9,23,24), has an excellent value for correct detection of a person at risk if it was only used for dichotomous classification. However, comparable to the EPOS predictive model (7), the high −LR of 19.0 demonstrates that the model is not suitable to rule out an increased risk of psychosis in patients with a negative test result. Furthermore, similar to the NAPLS (9) and the EPOS prediction model (7), our prognostic model showed a very low sensitivity, denying individuals at risk but scoring below threshold to access early intervention programs. Classification of individual prognostic scores to estimate the current risk of transition to psychosis is known to be a good alternative to overcome this problem with no loss of sensitivity (7,23).

Personalized risk estimation

Based on the prognostic scores of the five-variable EDIE-NL prediction model, i.e. the Cox regression equation, we identified three statistically distinct risk classes that are able to further classify the magnitude of the psychosis risk in selected risk groups.

The ilR in the highest class was almost 26 times higher than that in the lowest class, and >9 times higher than that in class II. Thus, compared with the 18-month general HR of 0.173 predicted by the UHR inclusion criteria, applying our model as a second step of risk stratification led to an important improvement in individual risk assessment. This included the ability to predict not only the magnitude of risk but also the time to transition, which differed markedly between class III and the other classes; the mean difference compared with the lowest class was ⩾8 months. In addition, in the sample with known outcome (**n** = 167), in the lowest class 3.9% of the subjects transitioned within 18 months, while in the highest risk class, about 80.0% transitioned within this time-frame. Therefore, the different risk classes may be useful to healthcare professionals to stratify and personalize treatment. For example, low index scores could be interpreted as indicating minimal risk, with little treatment necessary, i.e. monitoring of at-risk symptoms twice per year could be sufficient. High index scores could suggest CBT with additional outreach systemic treatment (i.e. talking to school teachers or coaching in the work situation, help with social relations and family support) to prevent withdrawal and exclusion. The future challenge is develop and test adequate interventions for each stratum of risk.

Predictors

All five predictors included in the EDIE prediction model have been linked to psychosis and are thus clinically meaningful. Two of the predictors found in the present study appear to be attenuated negative symptoms of psychosis, i.e. flattened affect and motor abnormalities. It is known that attenuated negative symptoms are an important part of the UHR status (6,29,30). The association between a higher degree of restricted affect and an increased risk of transition to psychosis confirms the results of a previous study (31) and appeared to correspond to one of the nine prodromal symptoms specified in the DSM-III-R (32) which did not, however, become part of the UHR criteria.

Another predictor variable was subjectively experienced impairment in motor function in the absence of any detectable behavioral abnormality. This was also one of the prodromal symptoms in DSM-III-R (32). Other researchers have also reported on disturbances in subjective motor functioning (30,33). Furthermore, subjective complaints of impaired motor functioning are also known as a basic symptom. Basic symptoms are defined as subtle, self-experienced, self-reported deficits that often remain solely in the self-perception of the patient and do not show in behavior (34,35). The basic symptoms are included in the CAARMS (3) and in the cognitive disturbances (COGDIS); both were previously found to be associated with high transition rates in UHR (36).

Next, the predictor variable PBIQ-R item subjectively experienced social marginalization is characterized by a person's cognitive appraisal of social participation. Thus, how a person attributes meaning to social disadvantage is linked to a higher risk of conversion.

The inclusion of SOFAS deterioration in social and role functioning as a predictor corresponds with findings showing that transition to first-episode psychosis is associated with reduced levels of social functioning (6,7,9,11,24,30,37–44). This is an interesting finding as the SOFAS criterion is already included in the UHR criteria. One possible explanation is that, independent of conversion to psychosis, patients may still experience significant levels of impaired social functioning (45,46); however, those patients that converted may have much poorer social functioning.

The association between a higher distress score associated with the CAARMS item non-bizarre ideas, and an increased risk of psychosis, corresponds with the results of recent studies. Both the NAPLS and the EPOS reported that suspicion predicted conversion (7,9). Another study showed that subclinical psychotic symptoms with distress and (eventually) with help-seeking behavior are more clinically relevant and have a higher risk for conversion (47,48). In contrast to our findings, i.e. that the distress associated with non-bizarre ideas is a predictor of psychosis, the study of Power et al. 2015 did not find such an association (49). One point of consideration is that perceptual abnormalities were rated the most distressing in their younger sample (18.5 years) compared to our older sample (22.7 years). Perceptual aberrations are prevalent in adolescence, but also highly transient. In our somewhat older sample, secondary delusions on the origin and power of auditory hallucinations may explain the higher distress (50).

In contrast to the NAPLS and the EPOS finding on positive symptoms, neither the total number of positive symptoms nor a specific positive symptom class were retained in the EDIE-NL prediction model. It has been shown that negative rather than positive symptoms can have a significant impact on the transition from a UHR state to a full-blown psychosis (30,44,51–53). In fact, positive symptoms may be transient and often remit without any treatment within 1 year from first presentation (47,52–55). It is important to note, however, that the EDIE-NL comprised a stage-dependent sample of only stage-1b UHR patients, recruited via a two-step screening procedure in secondary mental healthcare (56). Therefore, the variance in positive symptoms between patients is small and lacks predictive power. In samples with more diverse characteristics, however, the symptoms may well have predictive value.

Furthermore, based on this study and other studies (EPOS, NAPLS, PACE400) it appears that a strong PPV can be achieved using psychopathological data alone, which should therefore (at the moment) be preferred to extensive neuroimaging batteries.

Effect of treatment

The EDIE-NL trial (12) was an RCT designed to study the benefits of add-on CBT, targeted at the prevention of psychosis in a help-seeking UHR population. The EDIE-NL demonstrated a statistically significant risk reduction with CBT of about 50% (15). Following Hosmer et al. (1999) (25), in the final prediction model we added treatment as a potential confounder.

Treatment showed a HR of 1.683 but had no significant additive predictive value. Because the predictive model was equally strong in the experimental and control group, this implies that the effect of CBT on reducing the transition rate did not operate via targeting these particular risk factors, but through some other mechanism (such as changing the appraisal of beginning positive symptoms to prevent delusional explanations).

Strengths

The strengths of this study are the large number of participants, the low dropout rate, and the precise and repetitive assessment of transition to psychosis. Because the predictors were assessed in clinical practice, the detection of UHR patients can probably be improved in clinical practice. Furthermore, the patients can be classified into different risk classes.

Limitations

The limited number of transitions did not allow to split the sample to validate the model. However, bootstrapping was used to assess the internal validity of the Cox model.

The final predictors were derived by a statistical approach, by screening potential predictors for association with conversion to full-blown psychosis in multivariate models within each assessment domain, and only those predictors that contributed uniquely to conversion in an overall (cross-domain) multivariate model were retained. This approach could lead to an overfitting. However, to circumvent this risk, and to check the internal validity, a bootstrap analysis was used. Nevertheless, these predictors should be replicated in an independent study with similar features.

Several studies have found duration of symptoms to be a strong predictor of transition to psychosis (6). However, symptom duration was not measured in the current study.

In this trial, about 19% of the patients identified with an UHR were not willing to participate (15). In this sense, patients who consent to participate in a RCT may differ in a substantial way from other samples. In the present study the identified predictors are conditional on our UHR sample of help-seeking persons with co-morbid disorders who, in addition, were willing to participate in a trial.

Conclusion

Our results suggest that predicting a first-episode psychosis in UHR patients is improved using a five-predictor stage 1b-dependent prognostic model, including negative symptoms (observed flattened affect, subjective impaired motor functioning), impaired social functioning, beliefs about social marginalization and distress associated with non-bizarre ideas in a two-step algorithm combining risk detection and stratification. When translating our findings to clinical practice, and in line with others (7,24,57), negative symptoms and social functioning should be incorporated in future UHR criteria to advance psychosis prediction.

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Supplementary Material

Supplementary Table S1. List of Domains and Variables Evaluated for the Multivariate Cox Proportional Hazard Model

Domain (No. of variables)	Predictor variables	Variables Retained After Individual Univariate Cox Regression ($p<0.20$)	Variables Retained After Multivariate Cox Regression Per Domain ($p<0.15$)	Variables Retained After Multivariate Cox Regression Across Domains, Block-wise ($p<0.05$)
Positive symptoms, CAARMS (No. 20)	4 symptoms (UTC, NBI, PAB, DIS), raw intensity score; cut-off, intensity score ≥3 for UTC, NBI, PAB; cut-off, intensity score ≥2 or ≥3 or ≥4 for DIS; scores in ARMS range for each subscale; total intensity score, raw score; total intensity score, cut-off score ≥12; absolute number of symptoms scoring ≥3 or ≥4 on intensity; distress, absolute number of symptoms causing distress; distress, absolute number of symptoms scoring higher than median	Non-bizarre ideas, raw intensity score; NBI ≥4; NBI ≥5; PAB ≥5; NBI score in ARMS range; DIS score in ARMS range; positive symptom raw total score; absolute number of positive symptoms ≥4; UTC distress; NBI distress; UTC distress scoring higher than median; NBI distress scoring higher than median; absolute number of symptoms with distress; absolute number of symptoms with distress higher than median	Raw intensity score of non-bizarre ideas; unusual thought content distress median; number of positive symptoms with distress	None
Negative symptoms, CAARMS (No. 18)	3 symptoms (alogia, avolition/apathy, anhedonia), raw intensity score; alogia/ avolition/ anhedonia, cut-off, score ≥3 or ≥4 on intensity; avolition/ anhedonia, cut-off score ≥5 on intensity; total score, raw intensity score; cut-off, intensity score ≥10; absolute number of symptoms scoring ≥3 or ≥4 on intensity	Avolition, raw intensity score; alogia, cut-off score ≥3 on intensity; avolition, cut-off score ≥3; total score, raw intensity; total score, cut-off ≥10 on intensity; absolute number of symptoms ≥3	Absolute number of negative symptoms ≥3 on intensity	None

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Cognitive change -attention/ concentration, CAARMS (No. 9)	2 symptoms (subjective cognitive change; observed cognitive change), raw intensity score; subjective experience, cut-off score ≥3 or ≥4 or ≥5 on intensity; total score, raw intensity score; cut-off, score ≥5 on intensity; absolute number of symptoms scoring ≥3 or ≥4 on intensity	Subjective cognitive change, raw score; total score, raw intensity; subjective cognitive change ≥2 on intensity; subjective cognitive change ≥3 on intensity; subjective cognitive change ≥4 on intensity; absolute number of symptoms scoring ≥3 on intensity	Total score, raw intensity score	None
Emotional disturbance, CAARMS (No. 11)	3 symptoms (subjective emotional disturbance; observed blunted affect; observed inappropriate affect), raw intensity score; observed blunted affect, cut-off score ≥2 or ≥3 on intensity; emotional disturbance, cut-off score ≥3 or ≥4 on intensity; total score, raw intensity score; cut-off, intensity score ≥7; absolute number of symptoms scoring ≥3 or ≥4 on intensity	Subjective emotional disturbance, raw intensity; observed blunted affect, raw intensity; observed blunted affect ≥2; subjective emotional disturbance ≥3; subjective emotional disturbance ≥3; subjective emotional disturbance ≥4; absolute number of symptoms ≥3; absolute number of symptoms ≥4; total score, raw intensity; total score, cut-off ≥7	Observed blunted affect intensity score ≥3; Subjective emotional disturbance intensity score ≥4	Observed blunted affect intensity score ≥3
Behavioral Change, CAARMS[a] (No. 8)	2 symptoms (disorganising/ odd/stigmatising behavior; aggression/dangerous behavior), raw intensity score; cut-off score ≥3 on intensity; total score, raw intensity score; total score, raw score; cut-off, score ≥5 on intensity; absolute number of symptoms scoring ≥3 or ≥4 on intensity	Aggression/dangerous behavior, raw intensity score; total score, raw intensity; aggression/ dangerous behaviour, cut-off ≥3 on intensity; absolute number of symptoms ≥3 on intensity; absolute number of symptoms ≥4 on intensity	Absolute number of symptoms ≥4 on intensity	None

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Motor / Physical Changes, CAARMS (No. 10)	4 symptoms (subjective complaints of impaired motor functioning/ informant reported or observed changes in motor functioning/ subjective complaints of impaired bodily sensation/subjective complaints of impaired autonomic functioning), raw intensity score; subjective complaints of impaired motor functioning, cut-off score ≥3 on intensity; subjective complaints of impaired autonomic functioning, cut-off score ≥3 on intensity; total score, raw intensity score; total score, cut-off, score ≥7 on intensity; absolute number of symptoms scoring ≥3 or ≥4 on intensity	Subjective complaints of impaired motor functioning, raw score; subjective complaints of impaired motor functioning ≥3; absolute number of symptoms ≥3	Subjective complaints of impaired motor functioning ≥3	Subjective complaints of impaired motor functioning ≥3
OCD symptoms, CAARMS (No. 3)	OCD symptoms, raw intensity score; cut-off score ≥2 or ≥3 on intensity	None	None	None
Dissocitive symptoms, CAARMS (No. 2)	Dissociative symptoms, raw intensity score; cut-off score ≥3 on intensity	None	None	None
Total score, CAARMS (No. 2)	Total score, raw score; cut-off score ≥67	Total score, raw; total score, cut-off ≥67	Total score, cut-off ≥67	None

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Affective symptoms, CAARMS/ BDI/ CDS (No. 19)	CAARMS 3 symptoms (depression/ suicidality and self-harm/ mania/ mood swings and liability), raw intensity score; mania/ suicidality/mood swings, cut-off score ≥2; depression/ suicidality/ mania/ mood swings, cut-off score ≥3 on intensity; depression, cut-off ≥4 on intensity; absolute number of symptoms scoring ≥3 or ≥4 on intensity; total score, raw intensity score; total score, cut-off score ≥11; BDI, total score; cut-off score ≥ 19; CDS, total score; CDS, cut-off score ≥12	CAARMS mania, raw intensity score; CAARMS depression, raw intensity score; CAARMS suicidality, raw intensity score; CAARMS mania ≥2 on intensity; CAARMS suicidality ≥ 2; CAARMS depression ≥ 3 on intensity; CAARMS suicidality ≥ 3 on intensity; CAARMS depression ≥ 4 on intensity; total score, raw; total score, cut-off ≥11; BDI, total score; BDI, cut-off ≥19; CDS, total score; CDS, cut-off ≥12	Mania raw intensity score; BDI total score; CDS total score	None
Anxiety symptoms, CAARMS and SIAS (No. 6)	CAARMS anxiety: total score; cut-off score ≥3 or ≥4; SIAS, total score; SIAS, social phobia ≥34; SIAS, social anxiety ≥43	SIAS, total score; SIAS, social phobia ≥ 34; SIAS, social anxiety ≥ 43	SIAS, social phobia ≥34	None
SOFAS score[b] (No. 2)	SOFAS, total score; SOFAS, centered (around 45)	SOFAS, total score; SOFAS, centered	SOFAS, total score	SOFAS, total score
Inclusion criteria (No. 4)	Relative with psychosis; first- or second-degree relative with psychosis; APS irrespective of any other criterion; genetic risk irrespective of any other criterion	APS irrespective of any other criterion; genetic risk irrespective of any other criterion	None	None
Demographic criteria (No. 8)	Age; gender; Dutch or minority; ethnicity; years of education; current work situation; marital status; surrounding address density, cut-off ≥2500	Age; current work situation; Dutch/minority; ethnicity	Age; current work situation; ethnicity	None

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Domain (No. of variables)	Predictor variables	Variables Retained After Individual Univariate Cox Regression (p<0.20)	Variables Retained After Multivariate Cox Regression Per Domain (p<0.15)	Variables Retained After Multivariate Cox Regression Across Domains, Block-wise (p<0.05)
Bullying (No. 3)	Bullying (y/n); bullying degree (mild vs. moderate or serious); bullying duration (years)	Bullying (y/n)	Bullying (yes/no)	None
Burden (No. 17)	PBIQ-R, total score; cut-off score ≥94; 5 PBIQ-R symptoms (control/ shame/ entrapment/ loss/ social marginalization): raw score; PBIQ-R control, cut-off score ≥16; PBIQ-R shame, cut-off score ≥19; PBIQ-R entrapment, cut-off score ≥21; PBIQ-R loss, cut-off score ≥25; PBIQ-R social marginalization, cut-off score ≥16; MANSA[c], total score; MANSA, cut-off score ≥49; CAARMS impaired tolerance to normal stress: raw intensity score; cut-off score ≥3 or ≥4 on intensity	PBIQ-R, total score; cut-off score ≥94; 5 PBIQ-R symptoms (control/ shame/ entrapment/ loss/ social marginalization): raw score; PBIQ-R control, cut-off score ≥16; PBIQ-R shame, cut-off score ≥19; PBIQ-R entrapment, cut-off score ≥21; PBIQ-R loss, cut-off score ≥25; PBIQ-R social marginalization, cut-off score ≥16; MANSA, total score; MANSA, cut-off score ≥49; CAARMS impaired tolerance to normal stress: raw intensity score; cut-off score ≥3 or ≥4 on intensity	CAARMS impaired tolerance to normal stress, intensity ≥3; PBIQ-R entrapment, cut-off score ≥21; PBIQ-R social marginalization, cut-off score ≥16	PBIQ-R social marginalization, cut-off score ≥16

Supplementary Table S1. List of Domains and Variables Evaluated for the Multivariate Cox Proportional Hazard Model

Domain (No. of variables)	Predictor variables	Variables Retained After Individual Univariate Cox Regression (p<0.20)	Variables Retained After Multivariate Cox Regression Per Domain (p<0.15)	Variables Retained After Multivariate Cox Regression Across Domains, Block-wise (p<0.05)
Alcohol and drug abuse, CIDI (No. 17)	Alcohol abuse, lifetime or past 12 months prior to baseline; alcohol dependence, lifetime-time; cannabis, frequent use in the past 12 months prior to baseline; cannabis abuse, lifetime or past 12 months prior to baseline; cannabis dependence, lifetime; cocaine, frequent use in the past 12 months prior to baseline; cocaine abuse, lifetime or past 12 months prior to baseline; cocaine dependence, lifetime; amphetamine, frequent use in the past 12 months prior to baseline; amphetamine abuse, lifetime or past 12 months prior to baseline; any frequent drug use in the past 12 months (yes/no); any drug abuse/ dependence, lifetime; any drug dependence, lifetime (yes/no); abuse of 2 or more drugs, lifetime	any drug abuse/ dependence; any drug dependence, life-time; cannabis abuse, lifetime or past 12 months prior to baseline; cocaine abuse, lifetime or past 12 months prior to baseline	any drug dependence, lifetime	None

Note: BDI, Beck Depression Inventory; CAARMS, Comprehensive of At-Risk Mental States; CDS, Calgary Depression Scale; CIDI, Composite International Diagnostic Interview; DIS, disorganized speech; NBI, non-bizarre ideas; OCD, Obsessive compulsive disorder; PAB, perceptual abnormalities; SOFAS, Social Functioning Assessment Scale; UTC, unusual thought content. [a] *CAARMS symptoms: 'social isolation' and 'impaired role function' were not taken into account for the analyses because of their overlap with the SOFAS.* [b] *To keep all β coefficients positive, SOFAS scores have been inverted by subtracting 100 (higher score indicates a lower level, e.g. an original score of 40 equals 60).* [c] *To keep all β coefficients positive, MANSA scores have been inverted by subtracting 84 (higher score indicate a lower level, e.g., an original score of 20 equals 64).*

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