European Psychiatry

www.cambridge.org/epa

Active treatment of affective disturbances may improve functional outcomes in patients in the early state of psychosis: Results of the PRONIA study

Raimo K. R. Salokangas[1], Julian Wenzel[2], Tiina From[1], Tuula Ilonen[1], Reetta-Liina Armio[1], Heikki Laurikainen[1], Lauri Tuominen[1,3], Maija Walta[1], Anne Ruef[4], Carolina Bonivento[5], Dominic Dwyer[4,6], Paolo Brambilla[7,8], Stephen Wood[6,9,10], Rachel Upthegrove[10,11], Stefan Borgwardt[12], Eva Meisenzahl[13], Marlene Rosen[2], Theresa Lichtenstein[2], Stephan Ruhrmann[2], Christos Pantelis[14], Rebekka Lencer[12,15], Alessandro Bertolino[16], Frauke Schultze-Lutter[13,17,18], Anita Riecher[19], Joseph Kambeitz[2], Lana Kambeitz-Ilankovic[2,4], Nikolaos Koutsouleris[4,20,21], Jarmo Hietala[1] and the PRONIA consortium

[1]Department of Psychiatry, University of Turku, Turku, Finland; [2]University of Cologne, Faculty of Medicine, University Hospital of Cologne, Cologne, Germany; [3]University of Ottawa Institute of Mental Health Research, University of Ottawa, Ottawa, Ontario, Canada; [4]Department of Psychiatry and Psychotherapy, Ludwig-Maximilian University, Munich, Germany; [5]Scientific Institute, IRCCS E. Medea, Pasian di Prato, Udine, Italy; [6]Orygen, The National Centre of Excellence in Youth Mental Health, Melbourne, Victoria, Australia; [7]Department of Neurosciences and Mental Health, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [8]Department of Pathophysiology and Mental Health, University of Milan, Milan, Italy; [9]Centre for Youth Mental Health, University of Melbourne, Melbourne, Victoria, Australia; [10]Department of Psychiatry, University of Oxford, Oxford, UK; [11]Institute for Mental Health University of Birmingham, Birmingham, UK; [12]Translational Psychiatry Unit (TPU), Department of Psychiatry and Psychotherapy, University of Luebeck, Luebeck, Germany; [13]Department of Psychiatry and Psychotherapy, Medical Faculty, Heinrich-Heine University, Düsseldorf, Germany; [14]Melbourne Neuropsychiatry Centre, University of Melbourne & Melbourne Health, Melbourne, Australia; [15]Institute for Translational Psychiatry, University of Muenster, Muenster, Germany; [16]Department of Translational Biomedicine and Neuroscience, University of Bari Aldo Moro, Bari, Italy; [17]Department of Psychology, Faculty of Psychology, Airlangga University, Surabaya, Indonesia; [18]University Hospital of Child and Adolescent Psychiatry and Psychotherapy, University of Bern, Bern, Switzerland; [19]Department of Psychiatry (Psychiatric University Hospital, UPK), University of Basel, Switzerland; [20]Max Planck Institute for Psychiatry, Munich, Germany and [21]Institute of Psychiatry, Psychology & Neuroscience, Department of Psychosis Studies, King's College London, London, UK

Abstract

Background and objectives. The functional outcome of patients with psychotic disturbances is associated with several overlapping premorbid, societal, neuropsychological, and clinical factors. Extracting the factors associated with functional outcomes is important for designing effective mental health interventions.

Methods. In a naturalistic prospective European multicentre study, we analysed the effects of sociodemographic, preadmission, admission, and postadmission precursors on functional outcomes in 296 patients with recent-onset psychosis (ROP) and 262 patients at clinically high risk of psychosis (CHR-P). Functioning was assessed with the Global Assessment of Functioning—symptoms and deficits version—at baseline and at the 9- and 18-month follow-ups.

Results. In the overall sample, male sex, childhood adversities, poor sociability, scholastic problems, neurocognitive deficits, and greater severity of baseline and follow-up symptoms were associated with poor functional outcomes. In contrast, a favourable work/educational situation and preadmission treatment for nonpsychotic disorders were associated with better functional outcomes. Among ROP patients, neurocognitive deficits and the severity of baseline and follow-up affective and psychotic symptoms were strongly associated with functional outcomes. Among CHR-P patients, premorbid sociability, previous treatment for affective disorders, and follow-up affective symptoms played more significant roles.

Conclusions. To improve functioning in patients in the early stages of psychosis, several factors should be considered, such as sex, childhood adversities, psychosocial development, baseline neurocognitive deficits, work/educational situation, clinical presentations, and follow-up symptoms. Personalized and integrated treatment and rehabilitation measures should be actively continued beyond the first admission period, with a particular focus on addressing both baseline and follow-up affective disturbances.

Research Article

Cite this article: Salokangas RKR, Wenzel J, From T, Ilonen T, Armio R-L, Laurikainen H, Tuominen L, Walta M, Ruef A, Bonivento C, Dwyer D, Brambilla P, Wood S, Upthegrove R, Borgwardt S, Meisenzahl E, Rosen M, Lichtenstein T, Ruhrmann S, Pantelis C, Lencer R, Bertolino A, Schultze-Lutter F, Riecher A, Kambeitz J, Kambeitz-Ilankovic L, Koutsouleris N, Hietala J, the PRONIA consortium (2025). Active treatment of affective disturbances may improve functional outcomes in patients in the early state of psychosis: Results of the PRONIA study. *European Psychiatry*, **68**(1), e151, 1–12
https://doi.org/10.1192/j.eurpsy.2025.10113

Received: 19 May 2025
Revised: 29 August 2025
Accepted: 31 August 2025

Keywords:
affective disturbances; functional outcomes; prospective follow-up; psychosis; risk to psychosis

Corresponding author:
Raimo K. R. Salokangas;
Email: raimo.k.r.salokangas@utu.fi

EUROPEAN PSYCHIATRIC ASSOCIATION

Introduction

Kraepelin [1] and Bleuler [2] outcomes in patients with psychosis have been studied extensively. Both clinical and functional outcomes are important. For everyday well-being, functional outcomes are often considered the most important factor by patients and caregivers [3]. Negative symptoms, poor premorbid psychosocial development, educational and occupational achievements, male sex, single marital status, and a lack of interpersonal networks have all been associated with a poor illness course and worse functional outcomes in patients with psychosis, particularly in those with schizophrenia [4–7]. Moreover, neurocognitive deficits and childhood adversities have been associated with functional outcomes in patients with psychosis [8–10].

The onset of psychosis is often preceded by milder-than-psychosis psychiatric disturbances, such as the prodromal stage [1], latent schizophrenia [2], pseudo-neurotic schizophrenia [11], basic symptoms [12], the basic symptom criterion "cognitive disturbances" [13, 14] and ultra-high-risk and clinical high risk of psychosis (CHR-P) [15, 16]. In follow-up studies, less than 30% of the patients seeking help for CHR-P have converted to psychosis [17, 18]; however, for patients meeting both ultra-high-risk and cognitive disturbance criteria, the conversion rate is higher [19]. A majority of nonconverted CHR-P patients, including those meeting cognitive criteria, experience other clinical disturbances and functional deficits in clinical settings [20, 21] and in community life [22].

CHR-P patients are characterized by clinical disorders, particularly affective disorders, impairments in working ability, and deficits in educational and social functioning [18]. In outcome studies of CHR-P patients, premorbid psychosocial adjustment, childhood adversities, negative and disorganised symptoms, neurocognitive deficits, depression, and poor employment/study situations have been shown to predict poor functional outcomes [23–26]. Lifetime affective diagnoses are very common in CHR-P patients [27]. Using combined clinical and neuroimaging machine learning modelling, Koutsouleris et al. [26] reported that persistent social functioning impairments were associated with an increased risk of psychotic, depressive, and anxiety disorders at follow-up in CHR-P patients.

In the present naturalistic study, we focused on functioning, which encompassed psychiatric symptoms and functional disability, over an 18-month follow-up period in patients in the early stages of psychosis. Using premorbid and baseline factors and follow-up symptoms as predictors, our aim was to identify the precursors associated significantly with functional outcomes at baseline (T0), 9 months (T1), and 18 months (T2) among recent-onset psychosis (ROP) and CHR-P patients. We used univariate and multivariate general linear models for repeated measures (GLMrm) and path analyses to analyse mediating processes between precursors and functioning. We suggest that premorbid psychosocial adjustment, childhood adversities and preadmission affective disturbances, together with clinical, functional, and neurocognitive characteristics at the first clinical assessment, provide the most relevant and necessary information for clinicians. This information is essential when planning and implementing interventions aimed at supporting functional recovery. The inclusion of follow-up symptoms in predictive models is justified, as the early phase of treatment extends through the first month postadmission, when individually tailored interventions should be adapted to meet the patient's changing needs. This strategy was used in a previous follow-up study of patients with CHR-P and patients with a recent-onset depression [26].

Material and methods

This study is part of the Personalized Prognostic Tools for Early Psychosis Management (PRONIA; https://www.pronia.eu/) study, carried out in five European countries. *All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.* All participants (if minors, also their guardians) provided their written informed consent prior to study inclusion. The PRONIA was registered at the German Clinical Trials Register (DRKS00005042) and approved by the local research ethics committees in each location.

PRONIA recruited young help-seeking patients with ROP, CHR-P, a recent-onset depression, and healthy controls between February 2014 and May 2016. The first publication resulting from the PRONIA study [26], along with the supplementary methods, provides a detailed description of the study protocol, sampling procedures (including the criteria for ROP and CHR-P patients) [27, 28], assessments of the examined factors, and analytical methods used. The present study included 296 ROP patients and 262 CHR-P patients. The methods of the present study are described in detail in the Supplementary Material. Baseline and follow-up assessments are briefly described in Figure 1.

Statistical analyses, described in detail in the Supplementary Material, are summarised as follows. First, to reduce the number of factors and heterogeneity of the scales, the Premorbid Adjustment Scale (PAS), the Structured Interview for Psychosis-Risk Syndromes (SIPS), and neurocognitive test scores were factorised. The following factor dimensions were derived and used as precursors for functional outcomes: the PAS Sociability and Scholastic performance; the SIPS mood and stress, negative, positive, and disorganised dimensions; cognitive domains of social cognition; processing speed; working memory; verbal learning (memory); attention, and the sum of these factors (global). These and other outcome precursors, sociodemographic backgrounds, lifetime nonpsychotic diagnoses, and medications are described in Table 1 and Figure 1. Differences in the distributions and mean scores of the precursors between ROP patients and CHR-P patients were tested with the χ^2 test and Mann–Whitney *U* test, respectively.

Associations between the precursor factors and follow-up functional outcomes, assessed using GAFsd at T0, T1, and T2, were analysed using a general linear model for repeated measures (GLMrm). Although GAFsd at T0 represents baseline functioning, it also represents an outcome factor in relation to the preadmission stage (PAS, CTQ, and previous treatment) and was therefore included in the conceptualisation of follow-up functional outcomes. In the univariate GLMrm analyses, background, preadmission, and clinical factors were introduced as independent precursor variables to predict follow-up functioning (Table 2). In multivariate GLMrm analyses, the explanatory variables that had an indicative ($p < 0.1$) association with functioning (Table 1), according to univariate GLMrm analyses, were included in the model (Stage 1). The factors with nonindicative ($p > 0.1$) associations with functioning were subsequently omitted one by one (Stage 2). Finally, follow-up symptoms were included in the model, and all nonsignificant ($p > 0.5$) variables were omitted (Stage 3, Table 3). After each modelling step, the effects of omitted variables were tested and included if they did not meet the omission criterion. The analyses were carried out for all patients and for the ROP and CHR-P groups separately.

To analyse mediation processes, path analyses were performed, and a PROCESS macro in SPSS (model template 4) by Hayes [36]

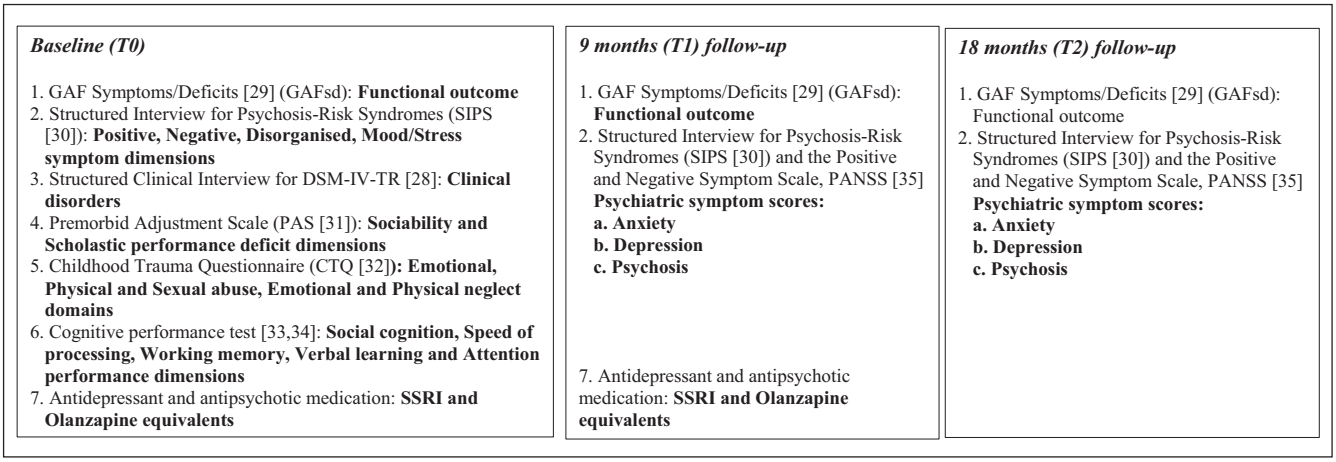

Figure 1. Study design with assessments at baseline and follow-up points.

Table 1. Distribution of background and means (SD) of PAS and neuropsychological test dimension scores, CTQ, SIPS, medication, and GAFsd scores by diagnosis (recent onset of psychosis, ROP; clinical high risk of psychosis, CHR-P)

	ROP	CHR-P	All	*p*1	*p*2	η^2
	n = 292	*n* = 262	*n* = 554		<0.001	0.057
Sex (%)*				0.040	0.005	0.022
Male	57.90	48.90	53.60			
Female	42.10	51.10	46.40			
Age (%)*				<0.001	0.320	0.003
14–20	17.10	29.80	23.10			
21–24	52.70	51.90	52.30			
25–40	30.10	18.30	24.50			
Mean (SD) §	24.5 (4.7)	22.9 (4.0)	23.8 (4.4)	<0.001		
Marital status (%)*				0.058	0.074	0.009
Single	79.50	72.50	76.20			
Ever married	20.50	27.50	23.80			
Partnership (%)*				0.733	0.145	0.006
No	48.60	46.90	47.80			
Yes	51.40	53.10	52.20			
Education (%)*				0.290	0.006	0.029
No graduation	13,00	9,90	11,60			
Graduation	70,90	76,70	73,60			
University degree	16,10	13,40	14,80			
Work situation (%)*				<0.001	<0.001	0.123
Not working	13.40	1.90	7.90			
Employed	41.10	66.40	53.10			
Unemployed	18.20	16.00	17.10			
Unable to work (long-term illness or disability	27.40	15.60	21.80			
PAS dimensions; mean (SD) §						
Sociability (problems)	−0.04 (0.99)	0.05 (1.01)	0.00 (1.00)	0.287	<0.001	0.057
Scholastic performance (problems)	0.01 (1.06)	−0.01 (0.93)	0.00 (1.00)	0.970	<0.001	0.046
CTQ scores; mean (SD) §						
Emotional abuse	4.90 (4.17)	5.54 (4.29)	5.20 (4.23)	094	0.020	0.015
Physical abuse	1.57 (2.74)	1.58 (2.82)	1.58 (2.78)	556	0.112	0.007

Continued

Table 1. *Continued*

	ROP	CHR-P	All	*p*1	*p*2	η^2
Sexual abuse	1.09 (2.80)	1.09 (2.64)	1.19 (2.72)	141	0.800	0.001
Emotional neglect	6.33 (4.15)	6.84 (4.16)	6.57 (4.16)	245	0.001	0.030
Physical neglect	2.64 (2.61)	2.49 (2.42)	2.572.52)	562	0.028	0.013
Sum	16.7 (12.4)	17.5 (12.4)	17.1 (12.4)	0.561	0.007	0.020
Lifetime non-psychotic diagnoses; mean (SD) §	0.66 (0.47)	0.59 (0.50)	0.62 (0.49)	0.026	0.013	0.017
0 (%)	66.10	56.90	61.70			
1 (%)	16.80	14.90	15.90			
2 (%)	9.60	14.10	11.70			
3+ (%)	7.50	14.10	10.60			
Neurocognitive (NEUCOG) dimension scores; mean (SD) §						
Social cognition	−0.10(0.99)	0.10(0.79)	−0.00(0.91)	0.008	0.001	0.029
Speed of processing	−0.13(0.51)	0.13(0.65)	−0.04(0.60)	<0.001	<0.001	0.077
Working memory	−0.17(0.77)	0.20(0.82)	0.01(0.81)	<0.001	<0.001	0.035
Verbal learning	−0.15(0.92)	0.21(0.72)	0.02(0.85)	<0.001	<0.001	0.050
Attention	−0.15(1.56)	0.020(1.48)	0.02(0.15)	0.007	0.003	0.024
Global	−0.13 (0.60)	0.16 (0.51	0.01 (0.57)	<0.001	<0.001	0.090
SIPS dimension scores; mean (SD) §						
Positive	0.59 (0.89)	−0.65(0.65)	0.00 (1.00)	<0.001	<0.001	0.068
Negative	0.03 (1.08)	−0.04(0.91)	0.00 (1.00)	0.515	<0.001	0.077
Disorganized	0.07 (1.17)	−0.08(0.76)	0.00 (1.00)	0.911	<0.001	0.082
Mood/stress	−0.01 (1.07)	0.01(0.92)	0.00 (1.00)	0.792	<0.001	0.050
Global	0.68(1.99)	−0.75(1.72)	0.00 (1.00)	<0.001	<0.001	0.273
Medication; mean (SD) §						
SSRI equivalents	10.42(24.26)	14.30(0.88)	12.56(26.37)	0.032	0.109	0.007
OLANZ equivalents	2.98(17.54)	1.36(8.46)	2.21(14.01)	0.181	0.973	0.000
GAFsd; mean (SD) §						
T0 (*n* = 554)	42.6 (13.0)	52.1 (11.4)	47.4 (13.2)	<0.001		
T1 (*n* = 360; ROP: *n* = 182)	60.6 (14.8)	64.5 (14.2)	62.5 (14.7)	0.011		
T2 (*n* = 360; ROP: *n* = 182)	62.0 (15.3)	65.7 (13.5)	63.9 (14.5)	0.023		

Abbreviations: CTQ, Childhood Trauma Questionnaire; GAFsd, Global Assessment of Functioning, Symptoms and Disability; OLANZ, olanzapine; PAS, Premorbid Adjustment Scale dimension scores; SIPS, Structural Interview of Prodromal Syndromes; SSRI, Serotonin selective reuptake inhibitor.
Note: Differences between ROP/CHR-P (χ^2 *and Mann–Whitney U test §: *p*1). Associations of each factor with follow-up functioning in a linear general model repeated measures (*p*2 and eta squared η^2).

was used. In the present study, we applied a prospective model to analyse the effects of preadmission precursor PAS and CTQ domains on follow-up functioning [GAFsdT1 + GAFsdT2], with neurocognitive and SIPS domains as mediators. We also analysed the indirect effects of neurocognitive and SIPS domains on follow-up functioning, with follow-up symptoms as mediators. The data were analysed using SPSS software (28.0 for Windows). *p* Values less than 0.05 (two-tailed) were considered to indicate statistical significance. Effect size is indicated by eta squared (η^2).

Results

Compared with CHR-P patients, ROP patients were more often males and older and were less likely to work. They also had more neurocognitive deficits and positive SIPS symptoms, and their GAFsd scores were lower at baseline and at follow-up (Table 1). A total of 50.0% of ROP patients and 43.1% of CHR-P patients had been treated for a lifetime nonpsychotic disorder (χ^2 = 2.621, p = 0.125). Lifetime affective disorders, depression, and anxiety were more prevalent among the CHR-P patients (38.9% vs. 22.9%, χ^2 = 16.647, p < 0.001) (Supplementary Table 1). CHR-P patients received antidepressant medication more often than ROP patients did, but there was no difference in the use of medication for psychosis (Table 1). Compared with females, males were more often single, lived less often in partnerships, and had lower education levels. Compared with males, females reported fewer problems with PAS scholastic performance (−0.27 vs. 0.23; p < 0.001) (Supplementary Table 2).

Compared with ROP patients, CHR-P patients had more depression at T1 and T2, and more anxiety at T2. There was no significant difference in psychotic symptoms (Supplementary Figure 2). Follow-up medication use was also not significantly different between

Table 2. Univariate general linear model repeated measures, main effects, for good follow-up functioning (GAFsdT0, GAFsdT1 and GAFsdT2) to each factor separately in all and in recent onset of psychosis (ROP) and clinical high risk (CHR-P) patients separately

	All				ROP				CHR-P			
	Mean Square	F	*p*	η2	Mean Square	F	*p*	η2	Mean Square	F	*p*	η2
Female sex	**3212.749**	**8.011**	**0.005**	**0.022**	1242.804	2.860	0.093	0.016	**1285.352**	**3.918**	**0.049**	**0.022**
Age	398.821	0.975	0.324	0.003	735.129	1.681	0.196	0.009	288.625	0.865	0.354	0.005
Marital status[#]	1304.691	3.211	0.074	0.009	1141.412	2.623	0.107	0.014	180.899	0.541	0.463	0.003
Partnership[#]	869.201	2.133	0.145	0.006	689.885	1.577	0.211	0.009	213.863	0.640	0.425	0.004
Education[#]	**2073.956**	**5.131**	**0.024**	**0.014**	1613.564	3.731	0.055	0.020	927.429	2.810	0.095	0.016
Current work[#]	**18104.312**	**50.370**	**<0.001**	**0.123**	**6336.842**	**15.600**	**<0.001**	**0.080**	**8748.405**	**30.628**	**<0.001**	**0.148**
PAS dimensions												
Sociability	**8338.498**	**21.563**	**<0.001**	**0.057**	**2122.395**	**4.940**	**0.027**	**0.027**	**7853.534**	**27.015**	**<0.001**	**0.133**
Scholastic performance	**6689.329**	**17.095**	**<0.001**	**0.046**	**5886.170**	**14.401**	**<0.001**	**0.074**	1016.832	3.085	0.081	0.017
CTQ (low scores)												
Emotional abuse	**2206.824**	**5.465**	**0.020**	**0.015**	333.207	0.758	0.385	0.004	**3165.393**	**9.974**	**0.002**	**0.054**
Physical abuse	1032.175	2.535	0.112	0.007	24.885	0.056	0.813	0.001	**1578.308**	**4.836**	**0.029**	**0.027**
Sexual abuse	26.387	0.064	0.800	0.001	153.770	0.349	0.555	0.002	0.862	0.003	0.960	0.001
Emotional neglect	**4371.771**	**10.990**	**0.001**	**0.030**	**2656.103**	**6.225**	**0.013**	**0.033**	**2265.728**	**7.026**	**0.009**	**0.038**
Physical neglect	**1965.379**	**4.859**	**0.028**	**0.013**	**2121.882**	**4.939**	**0.028**	**0.027**	175.295	0.524	0.470	0.003
Sum	**2942.487**	**7.324**	**0.007**	**0.020**	1017.138	2.334	0.128	0.013	**2228.700**	**6.907**	**0.009**	**0.038**
Life-time non-psychotic diagnoses	**2525.072**	**6.267**	**0.013**	**0.017**	743.421	1.700	0.194	0.009	**4475.719**	**14.442**	**<0.001**	**0.076**
NEUCOG												
Social cognition	**4327.089**	**10.875**	**0.001**	**0.029**	**1882.438**	**4.368**	**0.038**	**0.024**	**1329.020**	**4.055**	**0.046**	**0.023**
Speed of processing	**11243.299**	**29.698**	**<0.001**	**0.077**	**5853.477**	**14.315**	**<0.001**	**0.074**	**3357.179**	**10.615**	**0.001**	**0.057**
Working memory	**5065.872**	**12.798**	**<0.001**	**0.035**	**6768.384**	**16.761**	**<0.001**	**0.085**	1.533	0.005	0.946	0.001
Verbal learning	**7353.353**	**18.881**	**<0.001**	**0.050**	**2905.522**	**6.832**	**0.010**	**0.037**	**2247.490**	**6.967**	**0.009**	**0.038**
Attention	**3508.213**	**8.766**	**0.003**	**0.024**	**3681.242**	**8.745**	**0.004**	**0.046**	126.681	0.379	0.539	0.002
Global	**13212.658**	**35.414**	**<0.001**	**0.090**	**7480.933**	**18.709**	**<0.001**	**0.094**	**2307.729**	**7.162**	**0.008**	**0.039**
Diagnosis CHR versus ROP	**8303.831**	**21.468**	**<0.001**	**0.057**								
SIPS dimensions (low scores)												
Positive	**9936.224**	**25.995**	**<0.001**	**0.068**	**3259.746**	**7.701**	**0.006**	**0.041**	131.075	0.392	0.532	0.002
Negative	**11262.753**	**29.753**	**<0.001**	**0.077**	**6567.919**	**16.220**	**<0.001**	**0.083**	**4262.026**	**13.699**	**<0.001**	**0.072**
Disorganized	**12042.549**	**31.998**	**<0.001**	**0.082**	**5772.337**	**14.101**	**<0.001**	**0.073**	**4880.038**	**15.864**	**<0.001**	**0.083**
Mood/stress	**7320.749**	**18.793**	**<0.001**	**0.050**	**4146.131**	**9.910**	**0.002**	**0.052**	**4336.338**	**13.957**	**<0.001**	**0.073**
Sum	**40058.392**	**134.378**	**<0.001**	**0.273**	**21376.868**	**66.252**	**<0.001**	**0.269**	**11007.840**	**40.352**	**<0.001**	**0.187**
Medication												
SSRI equivalents	1049.787	2.579	0.109	0.007	47.497	0.108	0.743	0.001	873.822	2.645	0.106	0.015
OLANZ equivalents	0.478	0.001	0.973	0.000	8.453	0.019	0.890	0.000	374.313	1.123	0.291	0.006

Note: Significant associations bolded.

Abbreviations: CTQ, Childhood Trauma Questionnaire; SIPS, Structural Interview of Prodromal Syndromes; SSRI, serotonin selective retake inhibitor; GAFsd, global assessment of functioning, symptoms and disability; T0, baseline examination; T1, 9 months; T2, 18 months; η^2, eta squared.

[#]Marital status: single/ever married; partnership: no/yes; education: no/graduation/university degree; current work: no/yes; PAS: premorbid adjustment scale dimension scores; NEUCOG: neurocognitive test dimension scores.

Table 3. Multivariate general linear model repeated measures for good follow-up functioning (GAFsdT0, GAFsdT1, and GAFsdT2) in all and diagnostic groups separately, including follow-up symptoms

	ALL				ROP				CHR-P			
	Mean square	*F*	*p*	η^2	Mean square	*F*	*p*	η^2	Mean square	*F*	*p*	η^2
Female sex	2028.417	11.625	0.001	0.033	1906.956	9.713	0.002	0.054	780.996	5.290	0.023	0.031
Education[#]	745.394	4.272	0.015	0.024								
Current work[#]	1790.464	10.262	<0.001	0.083	1087.657	5.540	0.001	0.089	683.710	4.631	0.004	0.077
PAS dimension												
Sociability	735.176	4.213	0.041	0.012					2482.943	16.818	<0.001	0.091
Life-time non-psychotic diagnoses	1241.687	7.116	0.008	0.020					3006.154	20.362	<0.001	0.109
NEUROCOG												
Social cognition									671.947	4.551	0.034	0.027
Working memory					2433.643	12.396	0.001	0.068				
Verbal learning	1035.485	5.935	0.015	0.017								
SIPS dimensions												
Positive (−)	4772.402	27.352	<0.001	0.074								
Negative (−)	1245.553	7.139	0.008	0.020	938.828	4.782	0.030	0.027				
Disorganized (−)	2841.271	16.284	<0.001	0.045	3723.301	18.965	0.000	0.100				
Mood/stress (−)	2168.484	12.428	<0.001	0.035	1974.013	10.055	0.002	0.056				
Follow-up symptoms												
Anxiety T1 (−)	2092.764	11.994	0.001	0.034	2249.798	11.459	0.001	0.063				
Depression T1 (−)	3451.848	19.783	<0.001	0.055	890.604	4.536	0.035	0.026	3206.672	21.720	<0.001	0.115
Psychosis T1 (−)									2844.547	19.267	<0.001	0.103
Depression T2 (−)	874.895	5.014	0.026	0.014					680.202	4.607	0.033	0.027
Psychosis T2 (−)	6273.911	35.957	<0.001	0.095	6499.851	33.107	<0.001	0.163				

Note: Significant associations only.
Abbreviations: NEUCOG, neurocognitive test dimension scores; PAS, Premorbid Adjustment Scale Dimension Scores; SIPS, Structural Interview of Prodromal Syndromes; GAFsd, Global Assessment of Functioning, symptoms and disability; η, eta squared; T1: 9 months' follow-up; T2: 18 months' follow-up.
[#]Education: no/graduation/university degree; #current work: no/yes.

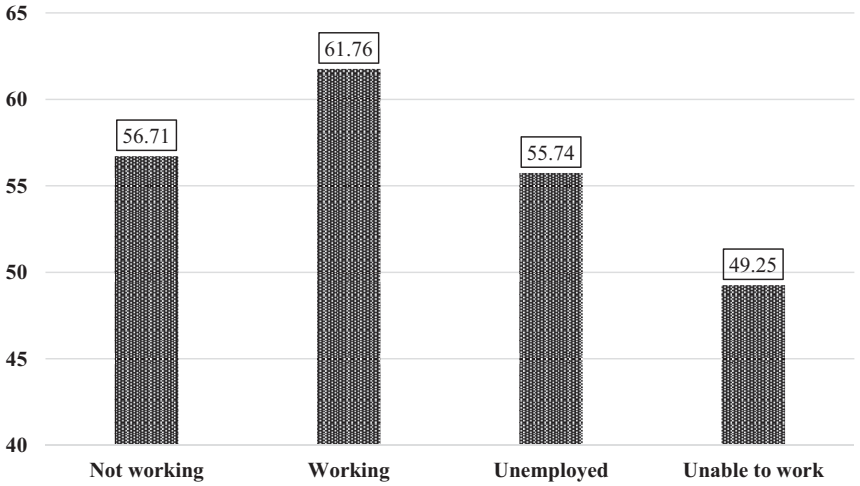

Figure 2. Functional outcome in univariate general linear model repeated measures of Global Assessment of Functioning, symptoms, and disability (GAFsdT0, GAFsdT1, and GAFsdT2) by current work situation in the whole sample (ROP and CHR-P). T0 = Baseline, T1 = 9 months follow-up, T2 = 18 months follow-up.
Significance of differences:
Not working versus Working ($p = 0.026$), Unemployed ($p = 706$), Unable to work ($p = 0.003$).
Working versus Unemployed ($p < 0.001$), Unable to work ($p < 0.001$).
Unemployed versus Unable to work ($p = 0.001$).

diagnostic groups (Supplementary Figure 3a). However, patients who received preadmission treatment for nonpsychotic disorders were more likely to receive both antidepressant and antipsychotic medication at T0 and T1 than were those who did not receive such treatment (Supplementary Figure 3b).

In the univariate rmGLM, female sex, good education and work situation, PAS sociability and scholastic performance, low emotional abuse, low emotional neglect and physical neglect scores, numerous lifetime nonpsychotic diagnoses, good performance in all the NEUPSY domains, and low scores in all the SIPS dimensions were associated with good functional outcomes (Table 2). In ROP patients, a good work situation, good PAS sociability and scholastic performance, low emotional and physical neglect scores, good performance in all the NEUPSY domains, and low scores in all the SIPS dimensions were associated with good functioning (Table 2). In the CHR-P patients, female sex, a good work situation, good sociability, low scores for emotional and physical abuse and emotional neglect, a high number of lifetime nonpsychotic diagnoses, better performances in social cognition, faster processing of verbal learning tasks, and low scores in all but the positive SIPS dimension were associated with good functioning. Medication was not associated with functional outcome (Table 2). However, the SSRI and OLANZ equivalents correlated with each other in all patients ($\rho = 0.196$; $p < 0.001$) and in ROP ($\rho = 0.232$; $p < 0.001$) and CHR-P ($\rho = 0.211$; $p = 0.001$) patients, indicating a combined use of SSRIs and OLANZs.

Patients with previous affective disorders had higher GAFsd scores at baseline, at T1 and at T2 (Supplementary Table 5). Patients who were working had the best functional outcomes, whereas those who were unable to work had the poorest functional outcomes. There was no difference between unemployed patients and those who did not work for other reasons (Figure 2).

Multivariate rmGLM analysis revealed that good functional outcomes were associated with female sex, good education and work status, high PAS sociability, lifetime nonpsychotic disorders, and good verbal learning. Poor functioning was related to high scores in all the SIPS dimensions, as well as elevated anxiety and depression at T1 and depression and psychotic symptoms at T2 (Table 3 and Supplementary Table 6a). In ROP patients, female sex, a good work situation, and good working memory were associated with good functioning, whereas high scores in the SIPS negative and disorganisation dimensions, high scores in mood/stress, high follow-up anxiety and depression at T1, and psychotic symptoms at T2, were associated with poor functional outcomes (Table 3 and Supplementary Table 6b). In the CHR-P patients, female sex, a good work situation, high PAS sociability, high social cognition, and a high number of nonpsychotic lifetime diagnoses were associated with good functioning, whereas depression at T1 and T2 and psychotic symptoms at T1 were associated with poor functioning (Table 3 and Supplementary Table 6c). Among the SIPS dimensions, only disorganized symptom scores correlated significantly with lifetime nonaffective disorders ($\rho = -0.238$; $p < 0.001$).

In path analyses, the precursors that were omitted in multivariate rmGLM were tested as mediators. The effect of PAS scholastic performance on functioning was mediated through certain NEUPSY and SIPS dimensions and follow-up symptoms. Some CTQ and NEUPSY components were associated with functional outcomes via certain SIPS and follow-up symptoms (Supplementary Table 7a-g).

The sensitivity analysis for functional outcome (limited to GAFsdT0 and GAFsdT1) indicated that the effect of depression at T2 in CHR-P patients and of the SIPS negative dimension in ROP patients became more pronounced over a longer follow-up period (Supplementary Table 8).

Discussion

According to the major results, in patients with early-stage psychosis, female sex, good neurocognitive performance, and good baseline work conditions were associated with good functional outcomes, whereas baseline and follow-up clinical symptoms were associated with poor functional outcomes. In ROP patients, severe baseline negative, disorganised, and mood/stress symptoms were associated with poor functional outcomes. In CHR-P patients, good childhood sociability and preadmission occurrence of affective disorders were associated with better functional outcomes. Furthermore, poor scholastic performance in childhood and childhood adverse experiences were indirectly associated with poor functional outcomes through other precursors.

Sex and functional outcomes in early psychosis

In agreement with the findings of several previous studies [4–7, 37, 38], male sex was associated with poor functioning at follow-up. Compared with female patients, male patients demonstrated poorer premorbid scholastic performance and adult education, partly explaining sex differences in functional outcomes. Thus, educational difficulties may present a special challenge for care systems aiming to rehabilitate male patients into occupational activities. Compared with females, males may prefer rehabilitative measures comprising physical (manual) and technical training and occupational or work rehabilitation supported by neurocognitive interventions [39]. Self-esteem and overall wellbeing are more closely related to satisfaction with daily occupations for men than for women [40]. To improve the functional outcomes of male patients, care services should consider their specific problems and needs, especially because psychosocial functional deficits are reported as the main driver of help-seeking males [41].

Effects of childhood adjustment and adversity on functional outcomes in early psychosis

In line with the findings of previous studies, patient premorbid adjustment is associated with functional outcomes [5, 6, 23, 42]. In the present study, childhood sociability, i.e., the ability to engage in and tolerate human social interaction, may be genetically programmed [43], explaining why its effect extends from childhood to adulthood in patients in the early state of psychosis. In contrast, the effect of scholastic problems on functional outcomes was mediated through neuropsychological deficits, baseline negative and disorganised symptoms, and follow-up depression and psychotic symptoms.

Childhood sociability and scholastic deficits are associated with negative symptoms, indicating that they may have their roots in early premorbid adjustment. In alignment with these findings, negative symptoms (such as flat affect) have been associated with poor premorbid sociability and poorer social and occupational outcomes in patients with first-episode psychosis or attenuated psychotic symptoms [44]. Clustering of difficulties in premorbid adjustment, negative symptoms, and poor functional outcomes is also detectable trans-diagnostically [42]. Accordingly, therapeutic and rehabilitative measures that aim to strengthen early social and educational functioning may improve the functional prospects of patients with psychosis and may also facilitate their clinical

recovery from negative symptoms. This approach is important for young patients, especially young males.

Multivariate analyses revealed that CTQ or its domains, particularly emotional and physical neglect, were not associated with functional outcome because their effects on functional outcome were mediated through other precursors, such as baseline negative symptoms and follow-up symptoms. Previous studies have shown that childhood adversities are associated with mental disorders among adults, such as depression, anxiety, and psychosis [45]. Our study revealed that the negative effect of childhood adversity extends through affective and psychotic disturbances to functional outcomes. Thus, when treating patients in the early state of psychosis, it is important to scrutinise their stressful and traumatic childhood experiences and start early trauma-focused psychotherapeutic interventions to facilitate their clinical and functional recovery [46].

Effects of work and educational situation on functional outcomes in early psychosis

Employment and work situation are among the most important factors that are repeatedly associated with functional outcome in patients with psychosis [1, 23, 47]. Indeed, work is an essential indicator of functioning. In the present study, approximately half of all patients were employed, with fewer employed ROP patients than CHR-P patients, and the baseline work situation was strongly associated with follow-up functioning in both patient groups. Consequently, in addition to effective interventions that alleviate neurocognitive deficits and clinical symptoms, direct work-related rehabilitation may enhance the work/employment status of patients with psychosis. Supported employment, which is based on the place-and-train strategy (individual placement and support; IPS), is an effective method for improving patients' ability to return to, or initiate, work or educational activities [48, 49]. In the present study, the patients who were not working or were unemployed (25%), as well as some of the patients who were on temporary sick leave, may be among those who would most benefit from IPS intervention. In addition to providing income, successful employment provides opportunities to build social support networks, engage in daily activities, and maintain the structure that is essential for individuals with severe mental illness [50]. The benefits of employment include increased self-esteem and self-confidence, experiences of success, greater independence, improved social integration and community participation, and reductions in negative and depressive symptoms, which all improve functioning and quality of life [51, 52].

Effects of neuropsychological performance on functional outcomes in early psychosis

In alignment with the findings of previous studies [8, 53–55], neuropsychological deficits are associated with poor functional outcomes in both ROP patients and CHR-P patients. Multivariate analyses revealed that the effects of neuropsychological deficits on functional outcomes were mediated mainly through baseline and follow-up clinical symptoms. The direct effect of the individual neuropsychological tests varied between diagnostic groups. Verbal learning and working memory deficits have repeatedly been associated with poor functioning in patients with severe psychosis (e.g., schizophrenia) [53], whereas deficits in social cognitive functioning are associated with poor functional outcomes in UHR patients [24]. Neurocognitive interventions, e.g., neurocognitive enhancement therapy or cognitive remediation, may essentially improve patients' capacity to cope with the requirements of various work tasks [56–59], while continuous work and occupational activities may maintain the positive effects achieved by neurocognitive interventions.

In severely disturbed patients, psychoeducation reduces relapses and readmission, promotes medication compliance, and improves overall well-being [60]. Additionally, less demanding work activities (e.g., sheltered employment), supported housing (e.g., rehabilitation homes), strong social support (e.g., caregivers), and assistance with daily routines, personal hygiene, appearance, and even transportation to the workplace may be needed [61]. No patient who has recovered from psychosis is unsuitable for supported employment.

Treatment of affective disorders may improve functional outcomes in the early state of psychosis

In ROP patients, the effect of the mood/stress dimension and follow-up anxiety and depression symptoms on functioning extended over the first nine follow-up months (T1), indicating that depression is intrinsic to the early stages of psychotic disorders [62]. Depressive symptoms during first-episode psychosis have been associated with poorer long-term global functioning [63], even across diagnostic categories [42]. Häfner et al. [38] suggested that affective disorders (depression) and schizophrenic psychoses may represent different stages of psychopathology rather than discrete illnesses. With respect to CHR-P patients, Van Oss and Guloksuz [64] suggested that the occurrence of subclinical psychotic or psychotic-like symptoms in clinical presentations mainly indicates the severity of affective symptomatology. Schultze-Lutter et al. [65] have criticised this conclusion for methodological reasons.

In line with previous studies [27, 66, 67], CHR-P patients were emblematically characterised by affective disturbances, particularly depression. There was a continuum of depression from baseline over the first nine follow-up months. Interestingly, CHR-P patients with preadmission treatment for nonpsychotic (90% affective) disorders formed a clinically less disturbed group with relatively good functional outcomes. They had received more antidepressants and antipsychotics than untreated patients, both at the time of admission and during the postadmission period. Most likely, CHR-P patients with a history of previous treatment had already developed a good treatment relationship that guaranteed more intensive care, including medication during follow-up, and supported functional outcomes. After admission, functioning improved much more in ROP patients than in CHR-P patients. It is possible that improving functioning in ROP patients was associated with the recovery, either spontaneous or due to antipsychotic treatment, of positive psychotic symptoms. In CHR-P patients, the effect of a reduction in psychotic-like symptoms on functioning was weaker, and because affective symptoms remained at a higher level during follow-up (Supplementary Figure 2), improvements in functioning were delayed. Overall, affective disorders, particularly depression, constitute a key target for the treatment of early-stage psychoses.

In ROP patients, positive symptoms can be successfully treated with antipsychotic drugs [68], which explains why baseline SIPS positive symptoms were not significantly associated with functional outcomes. However, at T2, psychotic symptoms were associated with decreased functioning, indicating that long-term treatment of psychotic symptoms and prevention of relapses are needed. In addition to antipsychotic drugs, family interventions, family

psychoeducation, and cognitive behavioural therapy are effective at reducing the risk of relapse or psychoses [69]. In CHR patients, attenuated psychotic symptoms were not directly associated with functioning at follow-up. However, SIPS positive, negative, and mood/stress symptoms were indirectly associated with functional outcomes through follow-up depression, emphasizing the need for treating depression both at admission and during the postadmission period.

In ROP patients, negative symptoms are strongly associated with interpersonal problems from childhood to adulthood. Interventions designed to improve social interaction skills and confidence may gradually reduce negative symptoms and, consequently, improve the overall functioning of patients recovering from psychosis. Antipsychotic drugs (e.g., aripiprazole), cognitive-behavioural therapy, skills-based training, and antidepressants, preferably combined with music and exercise therapy, as well as supported employment, may be effective in alleviating negative symptoms [59, 70, 71]. Disorganised symptoms are more narrowly associated with poor childhood sociability and impaired neurocognitive performance, indicating that interventions that improve cognitive performance, e.g., neurocognitive remediation, may accelerate the recovery of disorganised symptoms and create a foundation for improving functioning. Combining neurocognitive training programmes with psychosocial rehabilitative measures (e.g., IPS intervention) may reduce the detrimental effects of disorganised and negative symptoms on functioning and maintain positive results during neurocognitive training [72].

In CHR-P patients, early pharmacological and psychological interventions [73–77] reduce the conversion to psychosis, but fail to improve functional outcomes compared with those associated with comparative conditions [77]. In a review, CHR-P participants who received antidepressant treatment at baseline had a lower risk of transition than those who were not exposed to antidepressants [78]. However, compared with a psychosocial intervention (cognitive–behavioural case management) alone, fluoxetine medication did not improve young CHR-P patients' functioning [79]. Given that CHR-P patients are predisposed to both affective and psychotic disturbances, combined antidepressant and antipsychotic treatment may be necessary, particularly to improve functioning. If the clinical recovery of CHR-P patients is delayed, active treatment of psychosis is needed.

Advantages and limitations

The main advantage of this study is that it was conducted across five European countries, each with distinct psychiatric care systems. Thus, the results obtained can be considered practically generalizable to various European treatment systems. However, differences between countries were not analysed. The prospective study design with an 18-month follow-up encompassed an important treatment period for patients with early-stage psychosis. One limitation of the study was the lack of a comprehensive assessment of treatments received prior to baseline and during the follow-up period. Such information may have served as a moderator or mediator. Antidepressant and antipsychotic medications were administered at baseline and at the 9-month follow-up.

An important limitation is the moderately high drop-out rate (35%). Compared with psychotic patients in general, follow-up participants represent help-seeking patients in the early state of psychosis who have higher levels of education, better neurocognitive performance, better work situations, and better baseline functioning. Among the follow-up patients, differences between diagnostic groups remained similar to those observed at baseline. Because GAFsdT2 scores (at 18 months) were available for only 33% of the patients, the results of the GLMrms emphasize stage T1. In fact, the greatest clinical and functional changes occurred between baseline and T1; thereafter, the changes were smaller [34]. The significance of baseline negative symptoms and T2 depression symptoms was highlighted during the longer follow-up. In this study, we did not consider basic symptoms, and in the analyses, interactions were not considered. Retrospective preadmission data, such as childhood adversities, sociability, and scholastic success, are not as reliable as if they were obtained prospectively. However, they represent the real-world scenario when a clinician first evaluates a patient.

Conclusions

To improve functioning in patients in the early stages of psychosis, several factors should be considered. These include the patients' sex, childhood adversities, social adjustment, scholastic performance, baseline neurocognitive deficits, clinical presentation, and work/education status, as well as clinical symptomatology during the first follow-up months. Personalized, integrated interventions and rehabilitation measures should be actively continued after the first admission period, paying special attention to the treatment of affective disturbances. Additionally, longer monitoring of psychotic symptoms is necessary.

Supplementary material. The supplementary material for this article can be found at http://doi.org/10.1192/j.eurpsy.2025.10113.

Data availability statement. Requests for sharing the anonymized database should be addressed to the lead authors.

Acknowledgements. In addition to the description of the PRONIA consortium group at the end of Supplementary material, we have no acknowledgements.

Financial support. PRONIA is a Collaborative Project funded by the European Union under the 7th Framework Programme (grant 602152). The TEPS study was funded by Turku University Central Hospital (EVO funding).

Competing interest. The authors declare none.

References

[1] Kraepelin E. Psychiatrie: ein lehrbuch für studierende und ärzte. Leipzig: Verlag von Johan Ambrosius Barth; 1899.

[2] Bleuler E. Dementia praecox oder die gruppe der schizophrenien [Dementia praecox or the group of schizophrenias]. New York: International University Press; 1911/1950.

[3] Karambelas GJ, Filia K, Byrne LK, Allott KA, Jayasinghe A, Cotton SM. A systematic review comparing caregiver burden and psychological functioning in caregivers of individuals with schizophrenia spectrum disorders and bipolar disorders. BMC Psychiatry. 2022;22:422 https://doi.org/10.1186/s12888-022-04069-w.

[4] Salokangas RK. Prognostic implications of the sex of schizophrenic patients. Br J Psychiatry. 1983;142:145–51. https://doi.org/10.1192/bjp.142.2.145.

[5] Salokangas RK, Stengård E. Gender and short-term outcome in schizophrenia. Schizophr Res. 1990;3:333–45. https://doi.org/10.1016/0920-9964(90)90019-4.

[6] White C, Stirling J, Hopkins R, Morris J, Montague L, Tantam D, et al. Predictors of 10-year outcome of first-episode psychosis. Psychol Med. 2009;39:1447–56. https://doi.org/10.1017/s003329170800514x.

[7] Salokangas RKR, From T, Ilonen T, Luutonen S, Heinimaa M, Armio RL, et al. Short-term functional outcome in psychotic patients: results of the Turku early psychosis study (TEPS). BMC Psychiatry. 2021;21:602 https://doi.org/10.1186/s12888-021-03516-4.

[8] Pantelis C, Yücel M, Wood SJ, McGorry PD, Velakoulis D. Early and late neurodevelopmental disturbances in schizophrenia and their functional consequences. Aust N Z J Psychiatry. 2003;37:399–406. https://doi.org/10.1046/j.1440-1614.2003.01193.x.

[9] Rodriguez V, Aas M, Vorontsova N, Trotta G, Gadelrab R, Rooprai NK, et al. Exploring the interplay between adversity, neurocognition, social cognition, and functional outcome in people with psychosis: a narrative review. Front Psych. 2021;12:596949. https://doi.org/10.3389/fpsyt.2021.596949.

[10] Trotta A, Murray RM, Fisher HL. The impact of childhood adversity on the persistence of psychotic symptoms: a systematic review and meta-analysis. Psychol Med. 2015;45:2481–98. https://doi.org/10.1017/s0033291715000574.

[11] Hoch P, Polatin P. Pseudoneurotic forms of schizophrenia. Psychiatry Q. 1949;23:248–76. https://doi.org/10.1007/bf01563119.

[12] Huber G. Reine defektsyndrome und basisstadien endogener psychosen. Fortschr Neurol Psychiatr. 1966;34:409–26.

[13] Klosterkötter J, Hellmich M, Steinmeyer EM, Schultze-Lutter F. Diagnosing schizophrenia in the initial prodromal phase. Arch Gen Psychiatry. 2001;58:158–64. https://doi.org/10.1001/archpsyc.58.2.158.

[14] Schultze-Lutter F, Klosterkötter J, Picker H, Steinmeyer EM, Ruhrmann S. Predicting first-episode psychosis by basic symptom criteria. Clin Neuropsychiatry J Treat Eval. 2007;4:11–22.

[15] Yung AR, McGorry PD. The prodromal phase of first-episode psychosis: past and current conceptualizations. Schizophr Bull. 1996;22:353–70. https://doi.org/10.1093/schbul/22.2.353.

[16] McGlashan TH, Miller TJ, Woods SW. Structured interview for prodromal syndromes. Version 3.0. New Haven: Yale School of Medicine, PRIME Research Clinic; 2001.

[17] Simon AE, Velthorst E, Nieman DH, Linszen D, Umbricht D, De Haan L. Ultra high-risk state for psychosis and non-transition: A systematic review. Schizophr Res. 2011;132:8–17. doi:https://doi.org/10.1016/j.schres.2011.07.002.

[18] Fusar-Poli P, De Pablo GS, Correll CU, Meyer-Lindenberg A, Millan MJ, Borgwardt S, et al. Prevention of psychosis: Advances in detection, prognosis, and intervention. JAMA Psychiatry. 2020;77:755–65. https://doi.org/10.1001/jamapsychiatry.2019.4779.

[19] Schultze-Lutter F, Klosterkötter J, Ruhrmann S. Improving the clinical prediction of psychosis by combining ultra-high risk criteria and cognitive basic symptoms. Schizophr Res. 2014;154:100–6. https://doi.org/10.1016/j.schres.2014.02.010.

[20] Beck K, Andreou C, Studerus E, Heitz U, Ittig S, Leanza L, et al. Clinical and functional long-term outcome of patients at clinical high risk (CHR) for psychosis without transition to psychosis: a systematic review. Schizophr Res. 2019;210:39–47. https://doi.org/10.1016/j.schres.2018.12.047.

[21] Michel C, Ruhrmann S, Schimmelmann BG, Klosterkötter J, Schultze-Lutter F. Course of clinical high-risk states for psychosis beyond conversion. Eur Arch Psychiatry Clin Neurosci. 2018;268:39–48. https://doi.org/10.1007/s00406-016-0764-8.

[22] Michel C, Osman N, Rinaldi G, Schimmelmann BG, Kindler J, Schultze-Lutter F. Three-year course of clinical high-risk symptoms for psychosis in the community: a latent class analysis. Epidemiol Psychiatr Sci. 2025;34:e3 https://doi.org/10.1017/s2045796024000891.

[23] Salokangas RK, Heinimaa M, From T, Löyttyniemi E, Ilonen T, Luutonen S, et al. Short-term functional outcome and premorbid adjustment in clinical high-risk patients. Results of the EPOS project. Eur Psychiatry. 2014;29:371–80. https://doi.org/10.1016/j.eurpsy.2013.10.003.

[24] Glenthøj LB, Fagerlund B, Hjorthøj C, Jepsen JRM, Bak N, Kristensen TD, et al. Social cognition in patients at ultra-high risk for psychosis: what is the relation to social skills and functioning? Schizophr Res Cogn. 2016;5:21–7. https://doi.org/10.1016/j.scog.2016.06.004.

[25] Kraan TC, Ising HK, Fokkema M, Velthorst E, Van Den Berg DPG, Kerkhoven M, et al. The effect of childhood adversity on 4-year outcome in individuals at ultra high risk for psychosis in the Dutch early detection intervention evaluation (EDIE-NL) trial. Psychiatry Res. 2017;247:55–62. https://doi.org/10.1016/j.psychres.2016.11.014.

[26] Koutsouleris N, Kambeitz-Ilankovic L, Ruhrmann S, Rosen M, Ruef A, Dwyer DB, et al. Prediction models of functional outcomes for individuals in the clinical high-risk state for psychosis or with recent-onset depression: a multimodal, multisite machine learning analysis. JAMA Psychiatry 2018;75:1156–72. https://doi.org/10.1001/jamapsychiatry.2018.2165.

[27] Salokangas RK, Ruhrmann S, Von Reventlow HG, Heinimaa M, Svirskis T, From T, et al. Axis I diagnoses and transition to psychosis in clinical high-risk patients EPOS project: prospective follow-up of 245 clinical high-risk outpatients in four countries. Schizophr Res 2012;138:192–7. https://doi.org/10.1016/j.schres.2012.03.008.

[28] First MB, Spitzer RL, Gibbon M, Williams J. Structured clinical interview for DSM-IV-TR axis I disorders, research version. (SCID-I/P). New York: Biometrics Research, New York State Psychiatric Institute; 2002.

[29] Pedersen G, Hagtvet KA, Karterud S. Generalizability studies of the global assessment of functioning-Split version. Compr Psychiatry. 2007;48(1):88–94. https://doi.org/10.1016/j.comppsych.2006.03.008.

[30] McGlashan T, Walsh B, Woods S. The psychosis-risk syndrome: Handbook for diagnosis and follow-up. Oxford University Press; 2010.

[31] Cannon-Spoor HE, Potkin SG, Wyatt RJ. Measurement of premorbid adjustment in chronic schizophrenia. Schizophr Bull. 1982;8:470–84. https://doi.org/10.1093/schbul/8.3.470.

[32] Bernstein DP, Fink L. Childhood trauma questionnaire: a retrospective self-report. San Antonio: The Psychological Corporation, Harcourt Brace & Company; 1998.

[33] Wenzel J, Badde L, Haas SS, Bonivento C, Van Rheenen TE, Antonucci LA, et al. Transdiagnostic subgroups of cognitive impairment in early affective and psychotic illness. Neuropsychopharmacology. 2024;49:573–83. https://doi.org/10.1038/s41386-023-01729-7.

[34] Bonivento C, Kambeitz-Ilankovic L, Maggioni E, Borgwardt S, Lencer R, Meisenzahl E, et al. Neurocognitive skills and vulnerability for psychosis in depression and across the psychotic spectrum: findings from the PRONIA consortium. Br J Psychiatry. 2023;223:485–92. https://doi.org/10.1192/bjp.2023.98.

[35] Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13:261–76. https://doi.org/10.1093/schbul/13.2.261.

[36] Hayes AF. PROCESS procedure for SPSS release 3.4.1. http://www.processmacro.org; 2020.

[37] Jablensky A, Sartorius N, Ernberg G, Anker M, Korten A, Cooper JE, et al. Schizophrenia: manifestations, incidence and course in different cultures. A world health organization ten-country study. Psychol Med Monogr Suppl. 1992;20:1–97. https://doi.org/10.1017/s0264180100000904.

[38] Häfner H, Maurer K, Löffler W, Van Der Heiden W, Hambrecht M, Schultze-Lutter F. Modeling the early course of schizophrenia. Schizophr Bull. 2003;29:325–40. https://doi.org/10.1093/oxfordjournals.schbul.a007008.

[39] Medalia A, Saperstein AM. Does cognitive remediation for schizophrenia improve functional outcomes? Curr Opin Psychiatry. 2013;26:151–7. https://doi.org/10.1097/YCO.0b013e32835dcbd4.

[40] Eklund M, Hansson L, Bejerholm U. Relationships between satisfaction with occupational factors and health-related variables in schizophrenia outpatients. Soc Psychiatry Psychiatr Epidemiol. 2001;36:79–83. https://doi.org/10.1007/s001270050293.

[41] Osman N, Michel C, Schimmelmann BG, Schilbach L, Meisenzahl E, Schultze-Lutter F. Influence of mental health literacy on help-seeking behaviour for mental health problems in the Swiss young adult community: a cohort and longitudinal case-control study. Eur Arch Psychiatry Clin Neurosci. 2023;273:649–62. https://doi.org/10.1007/s00406-022-01483-9.

[42] Dwyer DB, Buciuman MO, Ruef A, Kambeitz J, Sen Dong M, Stinson C, et al. Clinical, brain, and multilevel clustering in early psychosis and affective stages. JAMA Psychiatry. 2022;79:677–89. https://doi.org/10.1001/jamapsychiatry.2022.1163.

[43] López-Tobón A, Trattaro S, Testa G. The sociability spectrum: evidence from reciprocal genetic copy number variations. Mol Autism. 2020;11:50 https://doi.org/10.1186/s13229-020-00347-0.

[44] Tarbox-Berry SI, Perkins DO, Woods SW, Addington J. Premorbid social adjustment and association with attenuated psychotic symptoms in clinical high-risk and help-seeking youth. Psychol Med. 2018;48:983–97. https://doi.org/10.1017/s0033291717002343.

[45] McKay MT, Kilmartin L, Meagher A, Cannon M, Healy C, Clarke MC. A revised and extended systematic review and meta-analysis of the relationship between childhood adversity and adult psychiatric disorder. J Psychiatr Res. 2022;156:268–83. https://doi.org/10.1016/j.jpsychires.2022.10.015.

[46] Coventry PA, Meader N, Melton H, Temple M, Dale H, Wright K, et al. Psychological and pharmacological interventions for posttraumatic stress disorder and comorbid mental health problems following complex traumatic events: systematic review and component network meta-analysis. PLoS Med. 2020;17:e1003262 https://doi.org/10.1371/journal.pmed.1003262.

[47] Tsang HW, Leung AY, Chung RC, Bell M, Cheung WM. Review on vocational predictors: a systematic review of predictors of vocational outcomes among individuals with schizophrenia: an update since 1998. Aust N Z J Psychiatry. 2010;44:495–504. https://doi.org/10.3109/00048671003785716.

[48] Modini M, Tan L, Brinchmann B, Wang MJ, Killackey E, Glozier N, et al. Supported employment for people with severe mental illness: Systematic review and meta-analysis of the international evidence. Br J Psychiatry. 2016;209:14–22. https://doi.org/10.1192/bjp.bp.115.165092.

[49] Rosenheck R, Mueser KT, Sint K, Lin H, Lynde DW, Glynn SM, et al. Supported employment and education in comprehensive, integrated care for first episode psychosis: effects on work, school, and disability income. Schizophr Res. 2017;182:120–8. https://doi.org/10.1016/j.schres.2016.09.024.

[50] Nicholson J, Wright SM, Carlisle AM. Pre-post, mixed-methods feasibility study of the working well mobile support tool for individuals with serious mental illness in the USA: a pilot study protocol. BMJ Open. 2018;8:e019936 https://doi.org/10.1136/bmjopen-2017-019936.

[51] Marwaha S, Johnson S. Schizophrenia and employment-a review. Soc Psychiatry Psychiatr Epidemiol. 2004;39:337–49. https://doi.org/10.1007/s00127-004-0762-4.

[52] Wallstroem IG, Pedersen P, Christensen TN, Hellström L, Bojesen AB, Stenager E, et al. A systematic review of individual placement and support, employment, and personal and clinical recovery. Psychiatr Serv. 2021;72:1040–7. https://doi.org/10.1176/appi.ps.202000070.

[53] Niendam TA, Bearden CE, Johnson JK, McKinley M, Loewy R, O'Brien M, et al. Neurocognitive performance and functional disability in the psychosis prodrome. Schizophr Res. 2006;84:100–11. https://doi.org/10.1016/j.schres.2006.02.005.

[54] Gebreegziabhere Y, Habatmu K, Mihretu A, Cella M, Alem A. Cognitive impairment in people with schizophrenia: an umbrella review. Eur Arch Psychiatry Clin Neurosci. 2022;272:1139–55. https://doi.org/10.1007/s00406-022-01416-6.

[55] Squarcina L, Kambeitz-Ilankovic L, Bonivento C, Prunas C, Oldani L, Wenzel J, et al. Relationships between global functioning and neuropsychological predictors in subjects at high risk of psychosis or with a recent onset of depression. World J Biol Psychiatry. 2022;23:573–81. https://doi.org/10.1080/15622975.2021.2014955.

[56] Bell M, Zito W, Greig T, Wexler BE. Neurocognitive enhancement therapy and competitive employment in schizophrenia: Effects on clients with poor community functioning. Am J Psychiatr Rehabil. 2008;11:109–22. https://doi.org/10.1080/15487760801963397.

[57] Chan JY, Hirai HW, Tsoi KK. Can computer-assisted cognitive remediation improve employment and productivity outcomes of patients with severe mental illness? A meta-analysis of prospective controlled trials. J Psychiatr Res. 2015;68:293–300. https://doi.org/10.1016/j.jpsychires.2015.05.010.

[58] Bell MD, Choi KH, Dyer C, Wexler BE. Benefits of cognitive remediation and supported employment for schizophrenia patients with poor community functioning. Psychiatr Serv. 2014;65:469–75. https://doi.org/10.1176/appi.ps.201200505.

[59] Lystad JU, Falkum E, Haaland V, Bull H, Evensen S, McGurk SR, et al. Cognitive remediation and occupational outcome in schizophrenia spectrum disorders: a 2 year follow-up study. Schizophr Res. 2017;185:122–9. https://doi.org/10.1016/j.schres.2016.12.020.

[60] Xia J, Merinder LB, Belgamwar MR. Psychoeducation for schizophrenia. Cochrane Database Syst Rev. 2011;2011:CD002831. https://doi.org/10.1002/14651858.CD002831.pub2.

[61] Kohn-Wood LP, Wilson MN. The context of caretaking in rural areas: Family factors influencing the level of functioning of seriously mentally ill patients living at home. Am J Community Psychol. 2005;36:1–13. https://doi.org/10.1007/s10464-005-6229-2.

[62] Upthegrove R, Lalousis P, Mallikarjun P, Chisholm K, Griffiths SL, Iqbal M, et al. The psychopathology and neuroanatomical markers of depression in early psychosis. Schizophr Bull. 2021;47:249–58. https://doi.org/10.1093/schbul/sbaa094.

[63] McGinty J, Upthegrove R. Depressive symptoms during first episode psychosis and functional outcome: a systematic review and meta-analysis. Schizophr Res. 2020;218:14–27. https://doi.org/10.1016/j.schres.2019.12.011.63.

[64] Van Os J, Guloksuz S. A critique of the "ultra-high risk" and "transition" paradigm World Psychiatry. 2017;16:200–6. https://doi.org/10.1002/wps.20423.

[65] Schultze-Lutter F, Klosterkötter J, Gaebel W, Schmidt SJ. Psychosis-risk criteria in the general population: frequent misinterpretations and current evidence. World Psychiatry. 2018;17:107–8. https://doi.org/10.1002/wps.20498.

[66] Fusar-Poli P, Nelson B, Valmaggia L, Yung AR, McGuire PK. Comorbid depressive and anxiety disorders in 509 individuals with an at-risk mental state: Impact on psychopathology and transition to psychosis. Schizophr Bull. 2014;40:120–31. https://doi.org/10.1093/schbul/sbs136.

[67] Falkenberg I, Valmaggia L, Byrnes M, Frascarelli M, Jones C, Rocchetti M, et al. Why are help-seeking subjects at ultra-high risk for psychosis help-seeking? Psychiatry Res. 2015;228:808–15. https://doi.org/10.1016/j.psychres.2015.05.018.

[68] Leucht S, Leucht C, Huhn M, Chaimani A, Mavridis D, Helfer B, et al. Sixty years of placebo-controlled antipsychotic drug trials in acute schizophrenia: systematic review, bayesian meta-analysis, and meta-regression of efficacy predictors. Am J Psychiatry. 2017;174:927–42. https://doi.org/10.1176/appi.ajp.2017.16121358.

[69] Bighelli I, Rodolico A, García-Mieres H, Pitschel-Walz G, Hansen WP, Schneider-Thoma J, et al. Psychosocial and psychological interventions for relapse prevention in schizophrenia: A systematic review and network meta-analysis. Lancet Psychiatry. 2021;8:969–80. https://doi.org/10.1016/s2215-0366(21)00243-1.

[70] Veerman SRT, Schulte PFJ, De Haan L. Treatment for negative symptoms in schizophrenia: a comprehensive review. Drugs. 2017;77:1423–59. https://doi.org/10.1007/s40265-017-0789-y.

[71] Lutgens D, Gariepy G, Malla A. Psychological and psychosocial interventions for negative symptoms in psychosis: systematic review and meta-analysis. Br J Psychiatry. 2017;210:324–32. https://doi.org/10.1192/bjp.bp.116.197103.

[72] Mucci A, Galderisi S, Gibertoni D, Rossi A, Rocca P, Bertolino A, et al. Factors associated with real-life functioning in persons with schizophrenia in a 4-year follow-up study of the Italian network for research on psychoses. JAMA Psychiatry. 2021;78:550–9. https://doi.org/10.1001/jamapsychiatry.2020.4614.

[73] McGorry PD, Yung AR, Phillips LJ, Yuen HP, Francey S, Cosgrave EM, et al. Randomized controlled trial of interventions designed to reduce the risk of progression to first-episode psychosis in a clinical sample with subthreshold symptoms. Arch Gen Psychiatry. 2002;59:921–8. https://doi.org/10.1001/archpsyc.59.10.921.

[74] McGorry PD, Nelson B, Phillips LJ, Yuen HP, Francey SM, Thampi A, et al. Randomized controlled trial of interventions for young people at ultra-high risk of psychosis: twelve-month outcome. J Clin Psychiatry. 2013;74:349–56. https://doi.org/10.4088/JCP.12m07785.

[75] McGlashan TH, Zipursky RB, Perkins D, Addington J, Miller T, Woods SW, et al. Randomized, double-blind trial of olanzapine versus placebo in patients prodromally symptomatic for psychosis. Am J Psychiatry. 2006;163:790–9. https://doi.org/10.1176/ajp.2006.163.5.790.

[76] Morrison AP, French P, Parker S, Roberts M, Stevens H, Bentall RP, Lewis SW. Three-year follow-up of a randomized controlled trial of cognitive

therapy for the prevention of psychosis in people at ultrahigh risk. Schizophr Bull. 2007;33:682–7. https://doi.org/10.1093/schbul/sbl042

[77] Schmidt SJ, Schultze-Lutter F, Schimmelmann BG, Maric NP, Salokangas RK, Riecher-Rössler A, et al. EPA guidance on the early intervention in clinical high risk states of psychoses. Eur Psychiatry. 2015;30:388–404. https://doi.org/10.1016/j.eurpsy.2015.01.013.

[78] Raballo A, Poletti M, Preti A. Do antidepressants prevent transition to psychosis in individuals at clinical high-risk (CHR-P)? Systematic review and meta-analysis. Psychol Med. 2023;53:4550–60. https://doi.org/10.1017/s0033291722001428.

[79] McGorry PD, Mei C, Amminger GP, Yuen HP, Kerr M, Spark J, et al. A sequential adaptive intervention strategy targeting remission and functional recovery in young people at ultrahigh risk of psychosis: The staged treatment in early psychosis (STEP) sequential multiple assignment randomized trial. JAMA Psychiatry. 2023;80:875–85. https://doi.org/10.1001/jamapsychiatry.2023.1947.