

Short report

Duration of untreated prodromal symptoms and 12-month functional outcome of individuals at risk of psychosis

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Summary

Individuals seeking help from prodromal services may have been experiencing attenuated psychotic features and psychosocial impairments for a long period prior to referral. The effect of an extended duration of these untreated 'at risk' symptoms on patients' long-term functional outcome was assessed in a 12-month longitudinal observational study ($n=49$). A longer duration of untreated 'at risk' symptoms was correlated with a reduced improvement in Global

Assessment of Functioning scores after 12 months ($\beta=-0.375$, $P=0.008$). This effect was independent of age and gender and may have implications for the improvement of treatment strategies in pre-psychotic phases.

Declaration of interest

None.

Recent systematic reviews and meta-analyses indicate that there is a consistent relationship between the duration of untreated psychosis and psychosocial outcome independent of other factors.^{1,2} However, many symptoms and a great deal of functional and social disability develop during the prodromal phase preceding the onset of first-episode psychosis.^{3,4} Neurobiological and neurocognitive changes may also occur during this pre-psychotic period.⁵ Although growing evidence suggests that a longer prodromal phase of psychosis is associated with poorer outcomes,⁶ such observations are based on retrospective studies and are clinically useless as preventive strategies. Psychopathological instruments are now available that allow the identification – in a longitudinal perspective – of individuals with 'at risk' symptoms (for a definition of 'at risk' symptoms see Method). As individuals who are at clinical risk for psychosis may or may not develop the disorder,³ the impact of the duration of their presenting symptoms on long-term functional outcome is mostly unknown.

Method

The setting of this longitudinal observational study was the outpatient service 'Programma 2000' based in Milan, Italy. This early-intervention clinical service provides 5 years of psychotherapy, psychoeducational and psychopharmacological interventions for individuals at clinical risk of psychosis. All patients at risk for psychosis assessed at the clinic between 2000 and 2006 were enrolled and followed up over a 1-year period. The inclusion criteria for being considered at clinical risk for psychosis have been developed by the Early Detection and Intervention programme of the German Research Network on Schizophrenia.⁷ Clinical assessment was performed using the Early Recognition Inventory (ERIRAos),^{8,9} which defines the prodromal state as one of the following: (a) presenting with certain self-experienced cognitive thought and perception deficits ('basic symptoms' according to Klosterkötter *et al*.⁴); and/or (b) demonstrating a clinical decline in functioning in combination with other well-established risk factors.³ Exclusion criteria were: being aged <18 and >36, presenting with any medical conditions or any previous diagnosis of a schizophrenic, schizophreniform, schizoaffective, delusional, bipolar or brief psychotic disorder according to DSM-IV.⁷ Socio-demographic characteristics were recorded via an unstandardised questionnaire and clinical assessment was conducted by two psychiatrists. Psychopathological characteristics

of the sample were collected by using the Brief Psychiatric Rating Scale (BPRS)¹⁰, ERIRAos,⁸ Global Assessment of Functioning (GAF)¹¹ and Health of the Nation Scale (HoNOS)¹² instruments at baseline (first contact with the prodromal service), 6 and 12 months. Duration of untreated 'at risk' symptoms was operationally defined as the first onset of specific basic symptoms as assessed using ERIRAos: thought interference; thought perseveration; thought pressure; thought blockage; disturbances of receptive language; decreased ability to discriminate between ideas and perception and between fantasy and true memories; unstable ideas of reference (subject-centrism); derealisation; visual perception disturbance; and acoustic perception disturbance.⁷ All participants gave informed consent to be part of the study.

Descriptive statistics (means and standard deviations for continuous variables and relative frequencies for categorical variables) were computed. Mean and 95% confidence intervals (CIs) of BPRS, GAF, ERIRAos and HoNOS at baseline, 6 months and 12 months were also calculated. Repeated-measures ANOVA was used to assess changes in BPRS, GAF, ERIRAos and HoNOS scores over the three time points. Pearson's correlation coefficients (R) were computed to estimate the correlation between GAF change (GAF after 12 months – GAF at baseline) and baseline characteristics. The association between the primary outcome (GAF change) and predictors was assessed by a general linear regression analysis, after checking for collinearity. The choice between collinear variables was based on clinical considerations. Variation due to the association model was estimated by the R^2 statistic. SPSS V.15 for Windows was used for all statistical analyses. Two-tailed P -values <0.01 were considered statistically significant.

Results

Overall, 49 individuals (65% males) participated in the study (9 of the original sample of 58 participants did not complete the follow-up assessments). There were no significant socio-demographic differences between male and female participants (t -tests, $P>0.05$). Socio-demographic data and scores on the BPRS, GAF, HoNOS and ERIRAos at baseline, 6-month and 12-month follow-up are reported in online Table DS1. Repeated-measures ANOVA of clinical ratings across time points (baseline, 6 months and 12 months) showed a significant improvement in GAF ($F=48.86$, $d.f.=2$, $P<0.001$), HoNOS ($F=20.85$, $d.f.=2$, $P<0.001$), ERIRAos ($F=34.82$, $d.f.=2$, $P<0.001$) and BPRS ($F=31.11$, $d.f.=2$, $P<0.001$) scores over time.

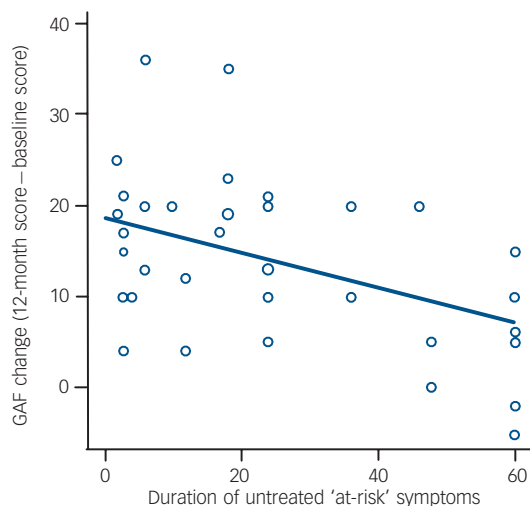


Fig. 1 Correlation between duration of untreated 'at risk' symptoms and change in Global Assessment of Functioning (GAF) score in individuals at clinical risk of psychosis.

A significant negative correlation between GAF score change over 12 months and duration of the untreated 'at risk' symptoms at baseline was observed ($r = -0.494$, $P = 0.001$; Fig. 1), but the correlations between GAF change and baseline BPRS, ERIRaos, HoNOS and age were non-significant ($r = -0.008$, $P = 0.960$; $r = -0.065$, $P = 0.683$; $r = -0.012$, $P = 0.938$; $r = -0.030$, $P = 0.849$ respectively).

We then built the regression model entering different factors (online Table DS2) and tested it, confirming that the duration of untreated 'at risk' symptoms was negatively associated with change in GAF scores (standardised β coefficient = -0.375 , $P = 0.008$). There was a moderate, albeit non-significant ($P > 0.01$), association between GAF outcomes at 12 months and being a graduate (standardised $\beta = 0.367$, $P = 0.012$) and being employed (standardised $\beta = 0.300$, $P = 0.030$). The model remained significant after adjusting for age, gender and symptoms (BPRS at 12 months – BPRS at baseline) and was able to explain 51% of the variance.

Discussion

The low predictive value and the high rate of false positives associated with the available assessment instruments for people at risk of psychosis have raised methodological criticisms and several ethical concerns regarding interventions in pre-psychotic phases.¹³ However, in line with evidence showing that preventive intervention in psychosis is feasible and effective, in our sample the global functioning of individuals at clinical risk for psychosis improved over the 12-month follow-up, presumably because of treatment. Despite these encouraging findings, young people seeking help from prodromal services may have been experiencing attenuated psychotic symptoms and psychosocial impairments for a long period before referral. In fact, we found that, on average, the first contact with prodromal services is preceded by a period of more than 2 years in which individuals are experiencing subtle and attenuated 'at risk' symptoms. In addition, we found that the duration of these untreated 'at risk' symptoms has a detrimental effect on long-term global functioning (Fig. 1). Previous cross-sectional studies have confirmed that individuals at risk for schizophrenia have significant functional deficits¹⁴ that precede overt symptom formation.¹⁵

Duration of untreated 'at risk' symptoms may be a potentially modifiable prognostic factor through a nationwide development

of prodromal services and a rapid referral of 'at risk' individuals. Although our study is limited by a small sample size and psychopathological heterogeneity across individuals at risk for psychosis, our findings support a very early detection of 'at risk' symptoms. Early diagnosis and early intervention services based in primary care and in the wider community (e.g. school counsellors, job centres and community youth centres) could improve long-term functioning of at-risk individuals independent of clinical outcome. A selective focus on the general functioning of the patient instead of their symptomatic profile seems to be one of the most promising end-point measures in future preventive interventions. Understanding the mechanism by which the duration of untreated 'at risk' symptoms interacts with environmental and genetic factors leading to transition to psychosis will also shed light on the pathophysiology of the prodromal phases of psychoses and may help improve treatment strategies.

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References

- Perkins DO, Gu H, Boteva K, Lieberman JA (2005) Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. *Am J Psychiatry* 2005; **162**: 1785–804.
- Norman RMG, Lewis SW, Marshall M. Duration of untreated psychosis and its relationship to clinical outcome. *Br J Psychiatry* 2005; **187** (suppl 48): s19–23.
- Yung AR, Phillips LJ, McGorry PD, McFarlane CA, Francey S, Harrigan S, et al. Prediction of psychosis. *Br J Psychiatry* 1998; **172** (suppl. 33): s14–20.
- Klosterkötter J, Hellmich M, Steinmeyer EM, Schultze-Lutter F. Diagnosing schizophrenia in the initial prodromal phase. *Arch Gen Psychiatry* 2001; **58**: 158–64.
- Fusar-Poli P, Perez J, Broome M, Borgwardt S, Placentino A, Caverzasi E, et al. Neurofunctional correlates of vulnerability to psychosis: a systematic review and meta-analysis. *Neurosci Biobehav Rev* 2007; **31**: 465–84.
- Keshavan MS, Haas G, Miewald J, Montrose DM, Reddy R, Schooler NR, et al. Prolonged untreated illness duration from prodromal onset predicts outcome in first episode psychoses. *Schizophr Bull* 2003; **29**: 757–69.
- Bechdolf A, Ruhrmann S, Wagner M, Kühn KU, Janssen B, Bottlender R, et al. Interventions in the initial prodromal states of psychosis in Germany: concept and recruitment. *Br J Psychiatry* 2005; **187** (suppl 48): s45–8.
- Maurer K, Horrmann F, Schmidt M, Trendler G, Hafner H. The early recognition inventory: structure, reliability and initial results. *Schizophr Res* 2004; **67** (suppl): 34.
- Häfner H, Maurer K, Ruhrmann S, Bechdolf A, Klosterkötter J, Wagner M, et al. Are early detection and secondary prevention feasible? Facts and visions. *Eur Arch Psychiatry Clin Neurosci* 2004; **254**: 117–28.
- Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychol Rep* 1962; **10**: 799–812.
- American Psychiatric Association. Multiaxial assessment. In *Diagnostic and Statistical Manual of Mental Disorders (4th edn, text revised) (DSM-IV-TR)*. APA, 2002.
- Wing JK, Beevor AS, Curtis RH, Park SB, Hadden S, Burns A. Health of the Nation Outcome Scales (HoNOS). Research and development. *Br J Psychiatry* 1998; **172**: 11–8.
- Cornblatt BA, Auther AM, Niendam T, Smith CW, Zinberg J, Bearden CE, et al. Preliminary findings for two new measures of social and role functioning in the prodromal phase of schizophrenia. *Schizophr Bull* 2007; **33**: 688–702.
- Ballon JS, Kaur T, Marks II, Cadenhead KS. Social functioning in young people at risk for schizophrenia. *Psychiatry Res* 2007; **151**: 29–35.
- Melle I, Haahr U, Friis S, Høstoft K, Johannessen JO, Larsen TK, et al. Reducing the duration of untreated first-episode psychosis: effects on baseline social functioning and quality of life. *Acta Psychiatr Scand* 2005; **112**: 469–73.

