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ORIGINAL PAPER

Relationship between duration of untreated prodromal symptoms and symptomatic and functional recovery

TianHong Zhang[1] · LiHua Xu[1] · YingYing Tang[1] · HuiRu Cui[1] · XiaoChen Tang[1] · YanYan Wei[1] · Yan Wang[1] · Qiang Hu[1] · ZhenYing Qian[1] · XiaoHua Liu[1] · ChunBo Li[1,2] · JiJun Wang[1,2,3]

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Abstract

Our previous study has found that a long duration of untreated prodromal symptoms (DUPrS) does not increase the conversion risk to psychosis in individuals with attenuated psychosis syndrome (APS). However, whether a long DUPrS will lead to other poor outcomes remains unknown. The purpose of this study was to analyse the association between the DUPrS and outcomes (symptomatic and functional recovery) in APS population. A post hoc analysis was performed in 391 individuals with APS as identified by the structured interview. APS subjects had follow-up interviews every 6 months for 2 years following diagnosis. Poor functional outcome was defined as a Global Assessment of Functioning (GAF) score less than 60 at the time of follow-up. Poor symptomatic outcome was defined as at least one of the positive symptoms rated scores of 3 or higher. A post hoc analysis was performed in 391 individuals with APS as identified by the structured interview. APS subjects had follow-up interviews every 6 months for 2 years following diagnosis. Poor functional outcome was defined as a Global Assessment of Functioning (GAF) score less than 60 at the time of follow-up. Poor symptomatic outcome was defined as at least one of the positive symptoms rated scores of 3 or higher. Of total 391 individuals, 334 were followed up for 2 years to assess clinical outcome, 82 (24.6%) had shown conversion to psychosis, 79 (23.7%) met the criteria of poor functioning outcome, and 145 (43.4%) met the criteria of poor symptomatic outcome. A significant correlation between GAF scores and DUPrS was observed in the non-converter group, but not in the converters. Individuals with APS who had a longer DUPrS were correlated with poorer functional outcome. However, it was not correlated with poorer symptomatic outcome. While a longer DUPrS was not related to poor symptomatic outcome, it was significantly related to poor functional outcome. Our findings highlight the importance of reducing DUPrS to decrease future functional impairment in populations at risk for psychosis.

Keywords Duration of untreated psychosis · Duration of untreated prodromal symptoms · Prodromal psychosis · Clinical high risk · Outcome

Introduction

The duration of untreated psychosis (DUP, the interval between the onset of psychosis and the initiation of treatment) is known to impact future functional outcomes [3, 10, 13], and, as a result, it has been identified as a key target for early intervention services for psychosis [11, 14]. In recent decades, the push for the early intervention strategies has led to many studies with the goal of identifying subthreshold levels of psychosis (attenuated psychosis syndrome, APS) [7, 8], but there is need for further investigation into a specific type of DUP among the APS population: the duration of untreated prodromal symptoms (DUPrS, the period between the onset of the first attenuated psychotic symptom

✉ TianHong Zhang
zhang_tianhong@126.com

✉ JiJun Wang
jijunwang27@163.com

[1] Shanghai Mental Health Center, Shanghai Jiaotong University School of Medicine, Shanghai Key Laboratory of Psychotic Disorders, 600 Wanping Nan Road, Shanghai 200030, People's Republic of China

[2] CAS Center for Excellence in Brain Science and Intelligence Technology (CEBSIT), Chinese Academy of Science, Beijing, People's Republic of China

[3] Bio-X Institutes, Key Laboratory for the Genetics of Developmental and Neuropsychiatric Disorders (Ministry of Education), Shanghai, People's Republic of China

and the commencement of professional help at psychiatric services) [22].

The close relationship between DUP and patients' outcomes, as well as the potential of DUP to be modifiable, raises the possibility of improving outcomes by shortening DUP. However, compared to DUP and psychosis, the relationship between DUPrS and outcomes in the APS population is relatively unknown. To our knowledge, only three studies have examined the relationship between DUPrS and Global Assessment of Functioning (GAF) [1] scores in APS individuals (sample size n = 49 [9], 73 [6], and 76 [5], respectively). Due to the highly heterogeneous nature of APS samples, the findings from these studies, that a longer DUPrS is associated with poorer functional recovery, needs to be replicated in a large, independent sample. In our first report [21], we analysed the baseline demographics and clinical factors contributing to DUPrS in APS individuals, and found no association between DUPrS and conversion to psychosis based on a 1-year follow-up. However, whether a long DUPrS leads to other poor outcomes such as poor functioning or residual symptoms remains unknown.

"Conversion" or "transition" has often been used as the main outcome of APS, but this has recently been questioned. Recently, van Os and Guloksuz [18] argued that the full range of person-specific psychopathology for at-risk youth should be considered rather than linking at-risk states and conversion to a transdiagnostic dimension of psychosis. The primary aims of the current study were to examine whether the length of DUPrS was related to functional or symptomatic outcomes. In particular, we hypothesized that results from this large Chinese APS cohort would support a close relationship between DUPrS and functional outcomes rather than symptomatic outcomes, similar to DUP in psychotic patients. If true, this would be an essential step in improving the understanding of the importance of shortening DUPrS in the pre-onset phase of psychosis.

Methods

Sample and procedure

This study was a post hoc analysis of a naturalistic follow-up study with a sample of 391 APS subjects who was selected based on screening and semi-structured interviews. The Research Ethics Committee at the Shanghai Mental Health Centre (SMHC) approved the study in 2011 and in 2013. At intake, all the potential subjects were identified based on a two-stage (self-report screen and face-to-face interview) method. The Prodromal Questionnaire-Brief version (PQ-B, Loewy et al. 2011) is a 21-item self-report measure designed to screen for possible prodromal symptoms. The Structured Interview for Prodromal Symptoms (SIPS) and Scale of Prodromal Syndromes (SOPS, thus SIPS/SOPS) [12] were used to determine whether subjects met the criteria for putative prodromal syndrome (clinical high risk status) or the Presence of a Psychotic Syndrome (POPS). The total sample consisted of 391 APS subjects recruited from SMHC between 2011 and 2015. Inclusion criteria were: (1) age of 14–45 years; (2) individuals younger than 18 years had to be accompanied by either a parent or legal guardian; (3) capacity to provide informed consent or assent if under 18 years; and (4) must have completed at least 6 years of primary education. Those with severe somatic diseases, mental retardation, or dementia were excluded. Subjects were selected in a consecutive series from those seeking an initial appointment at the psychological counselling service centre according to the hospital register. Details regarding study procedures, study setting, and implementation of measurements and assessments are reported elsewhere [19, 22]. Over the next 2 years, APS subjects were re-assessed every 6 months by face-to-face interview or by telephone using SIPS/SOPS. Of the 391 APS subjects, 334 completed up to 2-year follow-up, and 82 had converted to psychosis. A total of 334 APS subjects who completed follow-up, which included 50 (50/82, 61.0%) converters and 127 (127/252, 50.4%) non-converters, were re-assessed through face-to-face, and the rest through telephone. There was no significant difference on conversion rates between those who were followed up through face-to-face or telephone ($\chi^2 = 2.779$, $p = 0.095$). The average DUPrS in subjects with APS was 156 ± 122 days [25% percentile = 56, median = 111, 75% percentile = 241, and range (2–674) days]. The average follow-up period in subjects with APS was 14.6 ± 6.9 months.

Assessment and criteria

The designation of APS was determined using SIPS/SOPS. Positive symptoms were keys for identifying APS. Symptoms are rated on a 0–6 scale, with 6 indicating "severe and psychotic", and 3–5 indicating a prodromal range of symptoms. In the follow-up, conversion to psychosis was determined by SIPS with a level 6 psychotic symptom.

The criteria for onset of DUP and DUPrS differ substantially; DUP is defined as the onset of psychosis (at a psychotic level of intensity), whereas DUPrS is defined as the onset of the first attenuated psychotic positive symptom. Therefore, the methods for assessing these conditions are based on different levels of symptom severity (Fig. 1).

Functional outcome was defined based on Global Assessment of Functioning (GAF) follow-up scores. Poor functional outcome was defined as a GAF score less than 60 at the last time of follow-up [2, 17]. Of those 334 individuals who were followed up for 2 years, 79 were met the criteria of poor functional outcome. Symptomatic outcome was defined based on positive symptoms follow-up scores from SIPS/

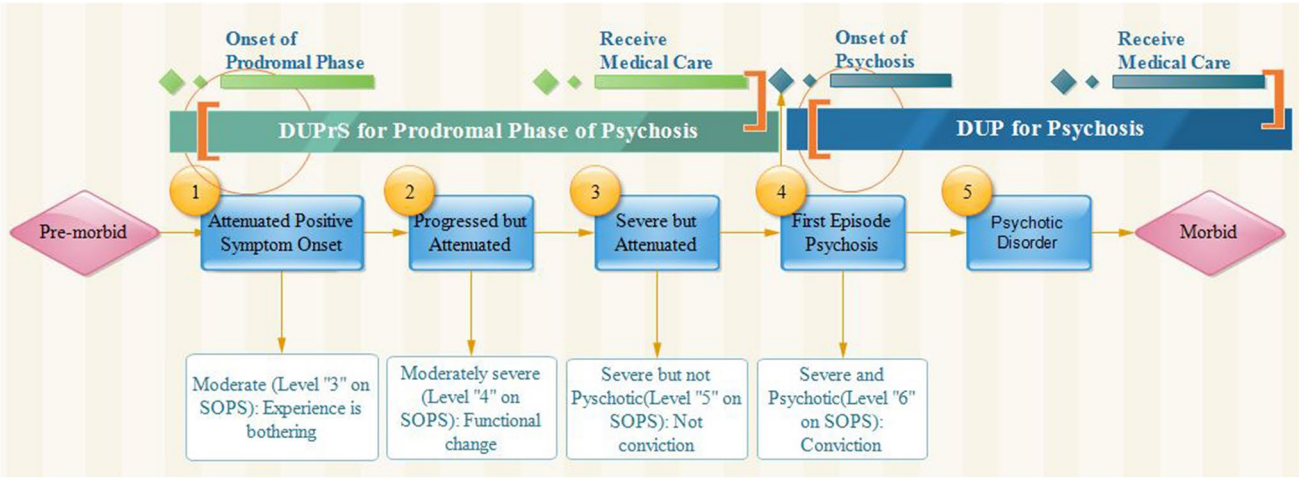

Fig. 1 Conceptual instruction for DUPrS (duration of untreated prodromal symptoms). DUPrS: duration of untreated prodromal symptoms; DUP: duration of untreated psychosis; SOPS: scale of prodromal syndromes, which is the main part of the structured interview for prodromal symptoms (SIPS). The SIPS consists of 19 items assessing four symptom domains: Positive symptoms (scales P1–P5, involving unusual thought contents, suspiciousness, grandiosity, perceptual abnormalities, and disorganized communication), negative symptoms, disorganized symptoms, and general symptoms. Only positive symptoms are used for identification of prodromal subjects. Each P item is rated on a 0–6 scale with 6 indicating "severe and psychotic" and 3–5 indicating a prodromal range of symptoms

SOPS. Poor symptomatic outcome was defined as at least one of the positive symptoms rated scores of 3 or higher. There were 145 individuals with APS which met the criteria of poor symptomatic outcome in this sample.

Data analysis

Data were summarized using standard descriptive statistics in SPSS version 16.0 (SPSS, Inc., Chicago, IL, USA) statistical software. Comparisons between participants who completed at least a 2-year follow-up and those who did not (called "lost" subjects) were made by the non-parametric Mann–Whitney *U* test. The correlation between DUPrS and GAF scores in the whole sample, converters, and non-converters was calculated by non-parametric Spearman's rank-correlation analysis for non-normally distributed data. Then, the relationship was explored via a partial correlation test, controlling for age and total score of positive symptoms. Of the 334 individuals with APS who completed at least a 2-year follow-up, we have divided them into two broad categories: functional recovery vs. poor functional outcome. Similarly, this sample is also grouped based on symptomatic outcome: symptomatic recovery vs. poor symptomatic outcome. The DUPrS for the outcome groups were displayed using histograms. Microsoft Excel was used to plot graphs. Comparisons between outcome groups were made by the non-parametric Mann–Whitney *U* test. Survival analysis (Kaplan–Meier) methods, along with log-rank tests, were performed to characterize the relationship of DUPrS with either poor functional outcome or poor symptomatic outcome over time. Finally, multivariate analyses with Cox proportional hazard regression models were performed to determine the hazard ratio of baseline severity of positive symptoms and DUPrS for predicting either poor functional outcome or poor symptomatic outcome. All reported results were two-tailed; significance was assumed at $p < 0.05$.

Results

Demographic information can be found in Table 1. No significant differences were found between individuals with APS who completed the follow-up and those who did not, for most variables. The only significant difference found was that individuals with higher baseline GAF scores were more likely to be lost during the follow-up than those with lower baseline GAF scores.

Table 2 highlights the significant negative correlation observed between DUPrS and GAF scores at past and follow-up interviews in individuals with APS (whole sample and non-converter groups) when controlling for age and severity of positive symptoms. Conversely, in the converter group, no significant correlation was found.

There was no significant difference in the DUPrS between poor symptomatic outcome group and symptomatic recovery group over the 2-year course of the study. However, a significant difference was found between poor functional outcome group and functional recovery group, which revealed that a longer DUPrS was correlated with poor functional outcome (Fig. 2).

Kaplan–Meier survival curves were constructed for 334 individuals with APS grouped by DUPrS length (> 111

Table 1 Demographics and clinical variables, comparing APS subjects who completed at least 1-year follow-up assessments and those who lost

Variables	Whole sample	Followed	Lost	Followed vs. lost	
				Z/χ^2	p
Cases (n)	391	334	57	–	–
Age (years), mean (SD)	20.4 (6.1)	20.2 (5.9)	21.6 (6.9)	−1.573	0.116
Male, n (%)	185 (47.3)	157 (47.0)	28 (49.1)	0.088	0.767
Education (years), mean (SD)	11.2 (3.0)	11.2 (3.0)	11.3 (3.0)	−0.770	0.442
DUPrS (day), mean (SD)	155.9 (121.7)	154.2 (121.9)	166.0 (120.9)	−0.790	0.430
SIPS/SOPS					
GAF past[a]	78.4 (4.8)	78.3 (4.9)	79.3 (4.2)	−0.891	0.373
GAF baseline[b]	55.2 (8.0)	54.7 (7.7)	57.9 (9.3)	−2.447	0.014
GAF follow-up[c]	–	68.6 (10.8)	–	–	–
Positive symptoms, [mean (SD)]	9.5 (3.6)	9.6 (3.7)	8.8 (3.2)	−1.438	0.150
Negative symptoms, [mean (SD)]	11.8 (5.9)	11.9 (5.9)	11.3 (6.0)	−0.734	0.463
Disorganized symptoms, [mean (SD)]	5.8 (3.2)	5.8 (3.1)	5.6 (3.6)	−0.893	0.372
General symptoms, [mean (SD)]	8.8 (3.2)	8.9 (3.3)	8.3 (3.1)	−1.529	0.126
Total score, [mean (SD)]	35.9 (11.1)	36.2 (10.9)	34.0 (12.2)	−1.192	0.233

[a]GAF past: the highest GAF score in the past year from the baseline

[b]GAF baseline: GAF score at baseline

[c]GAF follow-up: GAF score at final follow-up point. Non-parametric Mann–Whitney U tests were applied, because the variables did not fit the normal distribution

Table 2 Correlations of duration of untreated prodromal symptoms (DUPrS) with global assessment of functioning (GAF) score within the converter and non-converter groups

	DUPrS (Days)						
		Whole sample[a]	Converters[a]	Non-converters[a]	Whole sample[b]	Converters [b]	Non-converters[b]
GAF past[c]	r	−0.181	−0.015	−0.212	−0.181	−0.044	−0.223
	p	< 0.001	0.894	< 0.001	0.001	0.701	< 0.001
GAF baseline[d]	r	−0.008	−0.025	−0.012	0.009	0.019	0.028
	p	0.874	0.820	0.836	0.875	0.870	0.658
GAF follow-up[e]	r	−0.164	−0.179	−0.205	−0.106	−0.120	−0.154
	p	0.003	0.109	0.001	0.054	0.294	0.015

[a]Non-parametric spearman correlations were applied, because the variables did not fit the normal distribution

[b]Partial correlations were applied by control variables of age and the score of positive symptoms

[c]GAF past: the highest GAF score in the past year from the baseline

[d]GAF baseline: GAF score at baseline

[e]GAF follow-up: GAF score at final follow-up point

days vs. ≤ 111 days. The median DUPrS in subjects with APS was 111 days) using poor symptomatic outcome (at least one of the positive symptoms rated scores of 3 or higher at follow-up) as an endpoint. In addition, using poor functional outcome (a GAF score of less than 60 at follow-up) as an endpoint. Figure 3 shows that the rate of poor symptomatic outcome was not different between DUPrS groups (Log-rank test: $\chi^2 = 1.877$, $p = 0.171$), but the rate of poor functional outcome was significantly higher in individuals with APS with longer DUPrS (Log-rank test: $\chi^2 = 4.672$, $p = 0.031$).

Cox regression was used to evaluate the effect of the baseline severity of positive symptoms and DUPrS on poor symptomatic outcome or poor functional outcome. Consistently, DUPrS was found to significantly predict poor functional outcome in the model, and the baseline severity of positive symptoms was found to significantly predict poor symptomatic outcome (Table 3).

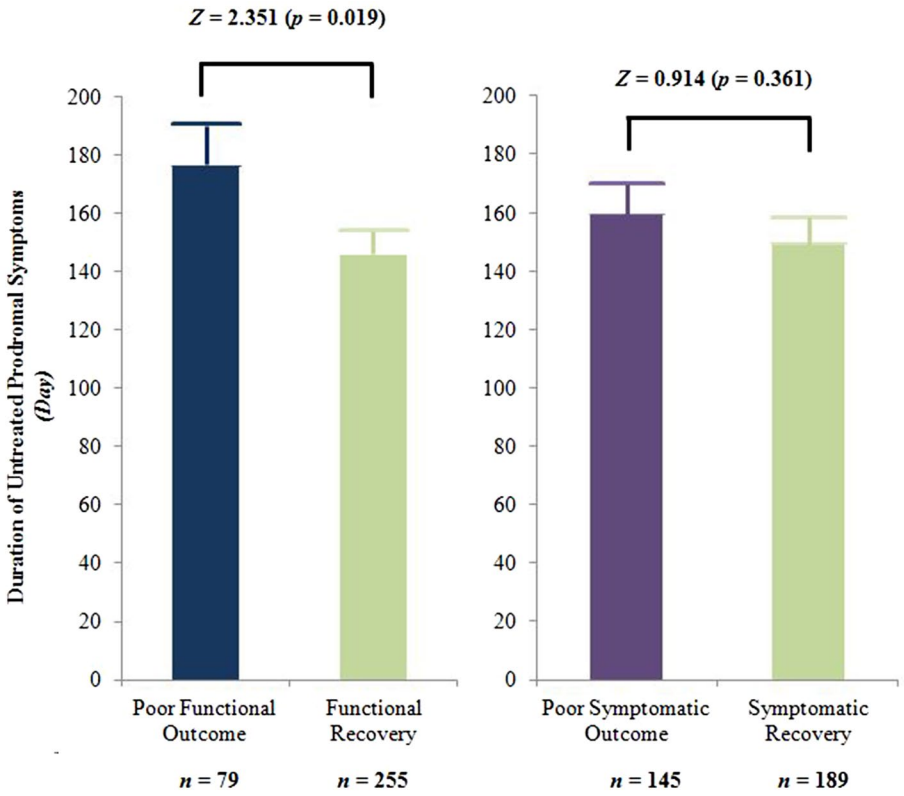

Fig. 2 Histogram of the duration of untreated prodromal symptoms across different outcome groups

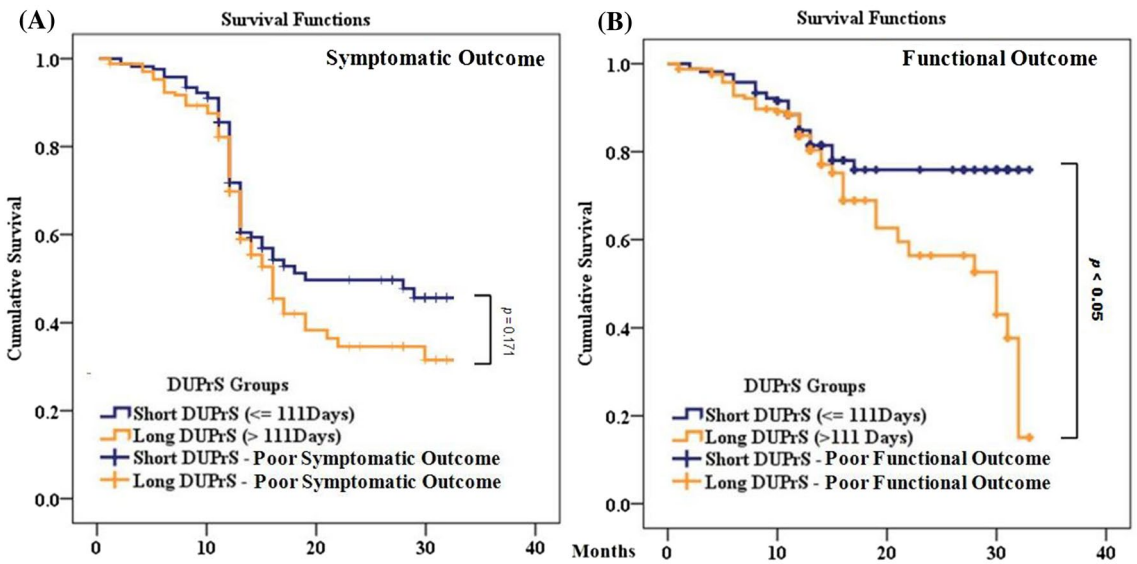

Fig. 3 Kaplan–Meier survival curves for symptomatic (**a**) and functional (**b**) outcomes in individuals with attenuated psychosis syndrome (APS) with a longer DUPrS (> 111 days) and those with a shorter DUPrS (≤ 111 days). The median DUPrS in subjects with APS was 111 days

Discussion

In contrast to the large body of research on DUP [4, 14–16], to our knowledge, a few studies have specifically examined the relationship between DUPrS and symptomatic or functional outcome in a large sample of individuals with APS. The relationship between DUP and functional outcome in patients with psychosis is consistently replicated in the pre-onset phase of psychosis; specifically,

Table 3 Cox regression for predicting the poor symptomatic outcome or poor functional outcome

Predictor variable	Beta	S.E.	Odds ratio	95% CI	Wald statistic	*p* value
Prediction of the poor symptomatic outcome						
Positive symptoms (*P* total score)	**0.083**	**0.022**	**1.086**	**1.040–1.135**	**13.687**	**< 0.001**
DUPrS	0.041	0.021	1.041	0.999–1.085	3.717	0.054
Prediction of the poor functional outcome						
Positive symptoms (*P* total score)	0.055	0.031	1.057	0.994–1.124	3.102	0.078
DUPrS	**0.062**	**0.029**	**1.064**	**1.006–1.125**	**4.680**	**0.031**

Bold in significant

in our study, longer DUPrS predicts poorer functional outcomes. However, DUPrS was not related to symptomatic recovery.

Our results suggest that, through APS identification and intervention services, DUPrS may be a potentially modifiable prognostic factor. However, it may be more reasonable for the aim of those services to be targeting functional recovery rather than symptomatic recovery [18]. Psychotic conversion may not be properly reflected in the core outcomes of APS, which places too much emphasis on transient positive symptoms, while the fundamental features of psychotic outcomes are generally permanent functional deficits. As proposed by van Os and Guloksuz [18], the concept of "conversion" should not be used as the only "outcome" in research or clinical practice, and more focus should be placed on functional recovery, especially for those with long DUPrS.

Our results may reflect another phenomenon that has not been reported in the literature. Due to the restricted available sample size of converters, no previous studies have compared converters with non-converters in terms of the relationship between DUPrS and functional levels. Interestingly, a significant correlation between DUPrS and functional levels was only found in non-converters, where a shorter DUPrS was associated with better functional levels at follow-up, and a longer DUPrS was associated with poorer functional level at follow-up. This phenomenon was not found among the converters. This observation suggests that the timeline for transient positive symptoms is different from that of functional deterioration in the APS population. We previously reported the results of this sample with 1-year follow-up, in which we find that a long DUPrS does not increase the conversion risk to psychosis [21]. Together with this study, in which we find that the DUPrS is not related to future symptomatic outcomes, it is possible that actual functional impairment is delayed relative to the transient positive symptoms, rather than occurring in parallel. On the other hand, the relationship between DUPrS and functional outcome in non-converters is less affected by transient positive symptoms, which led to the correlation which is more likely to be found.

There are several limitations of this study that need to be addressed. First, as in most APS follow-up studies, attrition (some at real risk for psychosis were lost to attrition), and limited follow-up period (some may develop psychosis in later phase) may bias our results. Although several methods were used to reduce the attrition rate, such as establishment of a 'WeChat' group to provide online support for APS families [20], there were 57 (14.6%) cases that were lost in the follow-up process. Second, information regarding DUPrS and past GAF scores was accessed retrospectively. We made a great effort to record the precise time of attenuated symptom onset during the SIPS interview, but recall bias could not be excluded. Third, our findings did not consider the severity of negative symptoms, emotional symptoms, or cognitive performances, which may have an influence on psychotic progression. Finally, individuals with APS in this study received a naturalistic treatment with different levels of compliance from their clinicians, and this may have confounded the results. However, none of designed intervention projects targeting APS have added value to this real-world information.

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Compliance with ethical standards

Conflict of interest None of the authors had a conflict of interest.

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