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Federated multi-site longitudinal study of at-risk mental state for psychosis in Japan

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ABSTRACT

There has been recent accumulation of evidence and clinical guidance regarding the at-risk mental state (ARMS) for psychosis. However, most studies have been observational cohort and intervention studies of Western populations. To assess the validity of the ARMS concept and the transition rate to psychosis in a non-Western nation, we retrospectively combined and analyzed clinical data of individuals diagnosed with ARMS who were prospectively followed-up at three specialized clinical services for ARMS in Japan. In total, we included 309 individuals with ARMS, of whom 43 developed overt psychosis. We estimated cumulative transition rates to psychosis with the Kaplan-Meier method, obtaining rates of 12% at 12, 16% at 24, 19% at 36, and 20% at 48 months. Only two individuals reported past cannabis use. Despite several differences among the three sites, transition rates did not differ among them. Furthermore, the transition rate of children aged between 14 and 17 years did not differ from that of individuals aged 18 years or older. Regression analysis revealed that meeting the brief limited intermittent psychotic symptoms (BLIPS) criterion was associated with an increased risk of transition to psychosis, whereas genetic risk factors were not. Although antipsychotic prescription was relatively frequent in this cohort, there was no evidence supporting frequent use of antipsychotics for this population. In conclusion, our findings support the assertion that the current concept of ARMS is applicable in Japan. Development of local clinical guidelines and training for clinicians is necessary to disseminate this concept to more clinical settings.

1. Introduction

In the last two decades, multiple studies have been published in which strategies have been developed for the clinical management of individuals with an at-risk mental state (ARMS) or who are at clinical high risk (CHR) for developing psychosis. More recently, clinical guidelines for ARMS have been published in the UK (National Collaborating Centre for Mental Health, 2014), Australia (Galletly et al., 2016), and Europe (Schmidt et al., 2015; Schultze-Lutter et al., 2015). However, contemporary methods for the ascertainment of psychosis risk states that have been developed and validated in Western nations have not been applied to large, multi-site samples to assess their validity and transition rate yield in Asian countries.

Currently, ARMS is most widely defined using the ultra-high risk (UHR) criteria (Fusar-Poli et al., 2013a; Yung et al., 1998). Indeed, guidelines in the UK (National Collaborating Centre for Mental Health, 2014) and Australia (Galletly et al., 2016) have primarily adopted these criteria to detect individuals with ARMS. However, the ability of the criteria to predict psychosis is limited (Fusar-Poli et al., 2012) and efforts to optimize ARMS identification continue.

These guidelines were developed from the results of several observational cohort and intervention studies in Western regions, including Europe, North America, and Australia. Data from other regions are scarce. In particular, large longitudinal cohort studies with >200 participants have been conducted in limited regions, including multicenter sites in Europe (Ruhrmann et al., 2010) and North America (Cannon et al., 2008; Cannon et al., 2016) and single sites in Melbourne (Nelson

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et al., 2013) and London (Fusar-Poli et al., 2013b) (see Supplemental Tables 1-1 and 1-2).

In Asia, longitudinal studies of ARMS have previously been conducted in several regions (Katsura et al., 2014; Kwon et al., 2012; Lam et al., 2006; Lee et al., 2013; Lim et al., 2015; Liu et al., 2011; Morita et al., 2014; Zhang et al., 2014; Zhang et al., 2017; see Table 1). Although these studies have generally replicated findings from Western regions, they have indicated some differences, including a lower rate of substance misuse (Katsura et al., 2014; Lam et al., 2006; Lim et al., 2015) and a higher rate of antipsychotic prescriptions during follow-up (Kwon et al., 2012; Liu et al., 2011; Morita et al., 2014; Zhang et al., 2017). However, relatively small sample sizes have been used and several methodological differences exist between the studies. Therefore, the validity and use of the ARMS concept in non-Western regions remain inconclusive.

Some factors potentially associated with the rate of transition to psychosis might differ among different regions of the world. For example, there may be differences in mental health care systems (affecting methods of recruitment (Fusar-Poli et al., 2016c), intervention strategies (e.g., antipsychotics prescription rates, access to psychological treatment), prevalence of exposure to potential risk factors (e.g., use of cannabis (Kraan et al., 2016)) and socio-cultural background (e.g., race and ethnicity (Fusar-Poli et al., 2016c)). Clinically oriented observations from diverse areas of the world are required to confirm the generalizability of the current clinical concept of ARMS, and to determine the need for any modifications to existing guidelines to suit local circumstances.

In Japan, several research centers are providing clinical services for individuals with ARMS. However, each study site has involved small sample numbers, limiting their statistical power. Therefore, we produced a large retrospective multi-site dataset by combining samples from three leading Japanese centers to ascertain the characteristics of individuals with ARMS in Japan, in comparison with previous studies from Western and Asian regions.

2. Methods

2.1. Design

We retrospectively combined clinical datasets of individuals with ARMS who were consecutively recruited and prospectively followed-up at specialized clinical services for ARMS at the Toho, Tohoku, and Toyama university hospitals. These hospitals are located across diverse areas in Japan, Tokyo, Sendai, and Toyama. The characteristics of each site have previously been described (Mizuno et al., 2009).

We obtained baseline characteristics and clinical features between 2004 and 2014, as well as data on the most recent clinical course in September 2014. Based on this, we estimated transition rates to psychosis during the follow-up period and examined if known risk factors were related to transition to psychosis in this population. Part of the data used in this study at Toho (Morita et al., 2014) and Tohoku (Katsura et al., 2014) have been reported previously.

The study protocol was reviewed and authorized by the ethics committee at each site, i.e., Toho University Ohmori Medical Center, Tohoku University Graduate School of Medicine and Tohoku University Hospital, and Toyama University.

2.2. Samples

Samples were consecutively recruited from 2004 at the Tohoku, 2006 at the Toyama, and 2007 at the Toho site up until March 2014. At the Tohoku and Toyama sites, all patients referred to specialized clinical services for ARMS were interviewed and screened for inclusion by trained psychiatrists. At the Toho site, all outpatients aged between 14 and 40 years old at the general psychiatric outpatient clinic at Toho University Hospital were screened with the Japanese version of the PRIME-Screen Revised (PS-R) (Kobayashi et al., 2008), and those positive for PS-R were additionally interviewed and screened for inclusion by trained psychiatrists.

Participants who met one or more of the UHR criteria were included in this study. UHR criteria comprise the attenuated psychotic symptom (APS), brief limited intermittent psychotic symptom (BLIPS), and the presence of genetic risk and functional decline (GRFD) criterions (Yung et al., 2003). At the Tohoku and Toyama sites, an assessment of UHR was made with the Comprehensive Assessment of At-Risk Mental State (CAARMS) (Yung et al., 2006), a semi-structured interview designed to evaluate comprehensive psychopathology and determine whether UHR criteria are met. We used the Japanese version, which has been validated at the Tohoku site with sufficient inter-rater reliability (Miyakoshi et al., 2009). At the Toho site, assessment was made with the Structured Interview for Prodromal Syndrome/the Scale of Prodromal Symptoms (SIPS/SOPS) (McGlashan et al., 2010), a structured interview and assessment instrument developed based on CAARMS. We used the Japanese version developed at the Toho site, which shows sufficient inter-rater reliability (Kobayashi et al., 2006). Although there are several differences between CAARMS and SIPS, the two instruments provide similar criteria for UHR, and excellent diagnostic agreement and comparability between the two have been reported (Fusar-Poli et al., 2016b). Additional inclusion criteria were being aged 14–35 years at the Tohoku and Toyama sites and 14–40 years at the Toho site.

Exclusion criteria that were common across the three sites were: 1) a history of psychotic disorder or manic episodes that fulfilled the diagnostic criteria of bipolar I disorder specified in the Diagnostic and Statistical Manual of Mental Disorders IV Text Revision (DSM-IV-TR) (American Psychiatric Association, 2000); 2) known intellectual disability; 3) neurological disorders, head injury, or any other significant medical conditions associated with psychiatric symptoms; and 4) fulfilling the criteria for substance abuse/dependence (at the Tohoku site, individuals fulfilling this criteria within 1 year of inclusion was also a planned exclusion criteria, but no one was excluded for this reason). At the Tohoku site, serious risk of suicide or violence due to personality disorder was exclusion criteria, but no one was excluded for this reason. All participants provided written informed consent, or if participants were under 18 at Tohoku and under 20 at Toyama and Toho, parents provided written informed consent while the participant gave written assent. Eligible participants who consented to enroll in the follow-up study were registered at each site.

2.3. Assessments

On the basis of previous studies (Cannon et al., 2008; Cannon et al., 2016; Fusar-Poli et al., 2013b; Nelson et al., 2013; Ruhrmann et al., 2010), we selected key baseline variable domains that characterize the ARMS cohort and/or contain variables potentially related to transition to psychosis (see Supplemental information). Among these domains, we identified common variables across sites that were consecutively collected at baseline or retrospectively examined using clinical records. However, because we used different measures of symptoms to identify ARMS, i.e., CAARMS and SIPS, it was impossible to collect common data for psychiatric symptoms. We also collected follow-up variable domains including type of intervention, hospitalization, and transition to psychosis (see Supplemental Information). Because several variables were coded in different ways across the sites, they were newly classified or re-classified according to coding styles defined for this study (see Supplemental information). All these variables were recorded according to a common format and then combined for analysis.

All participants were identified and clinically followed up by psychiatrists specifically trained in the assessment and treatment of ARMS (see Supplemental information). All assessments used in this study were conducted by trained psychiatrists except for the assessment of the CAARMS at the Toyama site. All psychiatrists and psychologists

Table 1
Summary of longitudinal studies of ARMS from Asian regions.

Location	Number of participants (baseline)	Male (%)	Mean age, years (age range criterium)	Substance abuse (%)	Number of participants (followed-up)	Follow-up duration	Transition rate (%)	Recruitment method	Followed-up by specialist clinic	Rate of antipsychotic prescription (%)
Hong Kong, China Lam et al., 2006	62	58.1	16.2 (9–25)	14.5	62[a]	6 months	29 at 6 months	Referrals from the specialized service for early psychosis	Monthly by specialist clinic	–
Taipei, Taiwan (SOPRES) Liu et al., 2011	59	55.9	21.5 (16–32)	–	57	21.8 months (mean) 0–53 months (range)	21.7 at 6 months[b] 28.2 at 12 months[b] 30.4 at 18 months[b] 33.3 at 24 months[b]	Mental health services and community population	By specialist clinic or other locations	79.7
Seoul, Korea Kwon et al., 2012	104	68.2	20.6 (15–35)	–	92	39.0 months (mean)	16.3	Mental health services and community population	By specialist clinic	64.1
Tokyo, Japan Morita et al., 2014	46	28.3	23.5 (16–40)	–	27	1 year	12	Outpatient clinic at a university hospital	By specialist clinic	77.8
Sendai, Japan Katsura et al., 2014	106	37.7	20.0 (14–35)	0	83	2.4 year[c] (mean)	7.5 at 6 months[b] 11.1 at 12 months[b] 15.4 at 24 months[b] 17.5 at 30 months[b]	Mental health services and community population	By specialist clinic	32.7[d]
Singapore (LYRINKS) Lee et al., 2013 Lim et al., 2015	173	67.6	21.3 (14–29)	10.4	–	1 year	3.5 at 6 months, 6.7 at 12 months	Hybrid approach: help-seeking and non-help-seeking individuals from psychiatric clinics and various community agencies	No	–
Shanghai, China Zhang et al., 2014	89	50.6	25.9 (15–45)	–	53	2 years	26.4 at 2 years	Screening at the largest psychological counseling clinic in Shanghai	No	–
Shanghai, China Zhang et al., 2017	117	47.9	24.7 (15–45)	–	86	2 years	29.1 at 2 years	As above	No	49.6

ARMS, at-risk mental state.
[a] Including 9 followed up by telephone.
[b] Using the Kaplan-Meier estimation.
[c] Mean follow-up period of all 106 cases.
[d] Rate of participants starting antipsychotics for the first time during follow-up.

involved in the study attended seminars and workshops to train in the assessment and treatment of ARMS. Inter-rater reliability of the CAARMS and SIPS/SOPS among the three sites was tested with video-recorded interviews of the use of each tool and were sufficient (ICC = 0.84 and 0.90, respectively).

Psychiatric disorders were diagnosed based on the DSM-IV-TR (American Psychiatric Association, 2000) and the diagnostic procedure at each site is described in the Supplemental information. Functioning was assessed with the Global Assessment of Functioning (GAF) scale (American Psychiatric Association, 2000). Regarding assignment of the three UHR criteria (APS, BLIPS, and GRFD), we allowed co-occurrence of each criterion in accordance with previous studies using SIPS/SOPS (Addington et al., 2015) or CAARMS (Fusar-Poli et al., 2013b; Lee et al., 2013; Yung et al., 2003).

Clinical examination of participants was undertaken by trained psychiatrists every 1–2 weeks in the initial months and thereafter on the basis of clinical need. Transition to psychosis was monitored at each examination in addition to the follow-up assessments conducted at 6 and 12 months at all three sites, as well as at additional assessments conducted at 18, 24, and 36 months at Tohoku, and 24 and 60 months at Toyama. All participants except four, whose final outcomes were confirmed via telephone interviews at the Tohoku site, were assessed face-to-face. For all participants, we used clinical records to collate all available data concerning whether they showed transition to psychosis and any interventions received, including antipsychotic medication and CBT.

At the Tohoku and Toyama sites, transition was defined by the CAARMS criteria (i.e., at least one fully positive psychotic symptom several times a week for more than one week). At the Toho site, the SIPS criteria (i.e., the presence of a positive symptom existing for more than one month or accompanying a serious disorganization or danger) were used. After transition to psychosis was confirmed, diagnosis of psychotic disorders was made by psychiatrists based on DSM-IV-TR (American Psychiatric Association, 2000) (see Supplemental information for a description of diagnostic procedures).

2.4. Interventions

The three centers used the same principle management strategy for ARMS. At each specialized clinic, the primary psychiatrist took the central role in treatment, collaborating with clinical psychologists and psychiatric social workers. Clinicians followed the principles of the International Clinical Practice Guidelines for Early Psychosis (International Early Psychosis Association Writing Group, 2005). All psychiatrists and psychologists involved in treatment had essential knowledge of the assessment and management of early psychosis, including ARMS, and had attended training workshops for this purpose. They were regularly supervised by the leading psychiatrist at each site (K.M., M.S., and M.M). Participants received the usual supportive counseling, symptom monitoring, psychosocial support, and crisis intervention. Additional psychoeducation, family counseling, and day care were offered, where appropriate. The frequency and duration of therapeutic sessions varied according to individual needs and phase of treatment. As is common in Japanese clinical settings, therapeutic sessions were continued as needed without limitation.

Among the 309 participants recruited to our study, 47 had also enrolled in open trials of antipsychotics (aripiprazole, $n = 36$; perospirone, $n = 11$) (Kobayashi et al., 2009; Tsujino et al., 2013) at the Toho site, and nine had enrolled in a trial of CBT (Matsumoto et al., 2018). While enrolled, these 56 individuals received specific trial interventions in addition to treatment as usual (as outlined above), and after the trial they were naturalistically followed up.

Antipsychotics, antidepressants, mood stabilizers, and/or anxiolytics were administered, if necessary. The use of antipsychotics was determined by the primary psychiatrist following the International Clinical Practice Guidelines for Early Psychosis (International Early Psychosis Association Writing Group, 2005). However, if individuals with ARMS were already taking antipsychotics prescribed by a previous psychiatrist and preferred to continue with them, they continued with the same treatment at least for the initial treatment phase. In this study, structured CBT was defined as individualized CBT delivered by a therapist other than the primary psychiatrist and following the manual by French and Morrison (French and Morrison, 2004). At Toho University, some participants received psychosocial interventions via a specialized daycare service, "Il Bosco" (Mizuno et al., 2012).

2.5. Data analysis

Statistical differences were determined with two-tailed tests, with a significance level *of* $P < 0.05$. Continuous variables are presented as means and standard deviations. Where appropriate, we calculated medians for continuous variables, and absolute and relative frequencies for categorical variables. We compared socio-demographic and clinical characteristics, follow-up duration, referral sources, and therapeutic interventions among the three sites with χ^2 tests for categorical variables and one-way ANOVAs for continuous variables. Furthermore, Games-Howell post-hoc tests were used to determine specific group differences.

Cumulative transition rates to psychosis over time were estimated with the Kaplan–Meier method. We considered transition as an event, and transition rates among the three sites were compared with the log-rank test.

A stepwise Cox regression analysis was planned to identify predictors for transition to psychosis. First, to identify potential risk factors

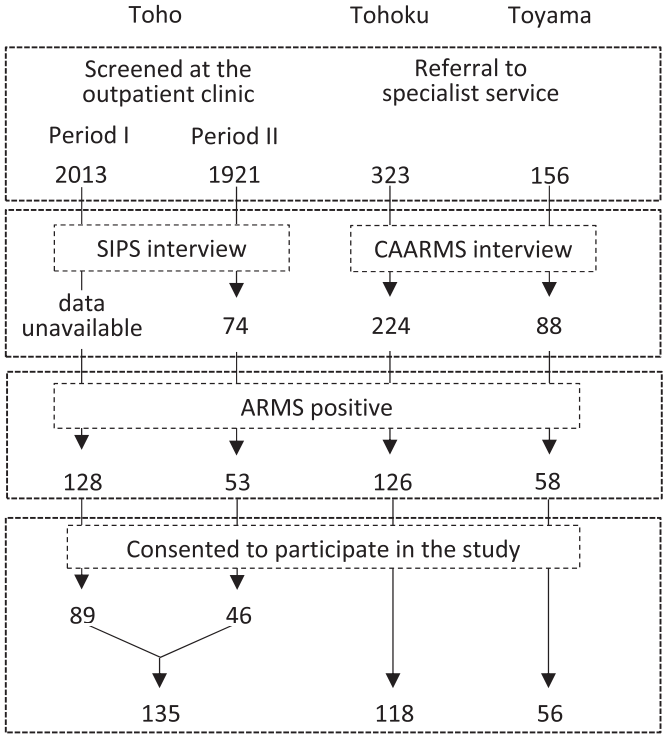

Fig. 1. Flow of participants through the study. At the Toho site, 1921 individuals were screened and 128 with ARMS were identified as fulfilling the inclusion and exclusion criteria during period I (January 2007–June 2010). However, the number of individuals completing SIPS interviews was unavailable. Among the individuals with ARMS, 89 consented to participate in the study. During period II (July 2010–March 2014), 2013 individuals were screened and 74 underwent a SIPS interview, with 53 fulfilling the inclusion and exclusion criteria. Of these, 46 consented to participate in the study. SIPS: Structured Interview for Prodromal Syndromes; CAARMS: Comprehensive Assessment of At-Risk Mental States; ARMS: at-risk mental state.

in an exploratory analysis, we used single-variable Cox regression analyses (with a cut-off point *of* $P < 0.10$) to compare all the available baseline demographic and clinical variables between individuals who transitioned to psychosis ("transitioners") and those who did not ("non-transitioners"). However, patients with present/past substance use and cannabis were omitted from analyses because of the small number of cases. Baseline variables included were gender, age, marital status, presence of housemates, school and work status, referral source, history of antipsychotic medication, genetic risk factors (having first-degree relative with psychotic disorder), BLIPS criterion (met or not, irrespective of co-occurrence of the other two criteria), GAF score, and year of enrolment. We included age because we were specifically interested in whether the transition rate of children (defined as under 18 years old in Japan) was different from that of adults, with age treated as a dichotomous variable of under 18 or 18 and over. Subsequently, we planned to perform multivariate Cox regression to determine possible predictors of transition.

Statistical differences were determined with two-tailed tests, with a significance level *of* $P < 0.05$. All statistical analyses were performed using SPSS 19.0 for Windows (IBM, Armonk: NY).

3. Results

3.1. Participants and ARMS subgroups

Fig. 1 shows the sample flow for the study. At the Toho site, 7 individuals of the 74 patients who were interviewed with the SIPS were diagnosed with psychosis during period II. At the Tohoku site, 79 of the 323 referrals and 25 of the 224 patients interviewed with the CAARMS were diagnosed with psychosis. At the Toyama site, 28 of the 156 referrals and 4 of the 224 patients interviewed with the CAARMS were diagnosed with psychosis.

In total, we analyzed data for 309 individuals with ARMS (Toho, $n = 135$; Tohoku, $n = 118$; and Toyama, $n = 56$) who had consented to participate in the follow-up study at each site (Table 2). In Fig. 2, we indicate the number of participants corresponding to each possible combination of the three UHR criteria in a Venn diagram. Most participants ($n = 294$; 95%) met the APS criterion and 73% ($n = 219$) met the APS criterion alone. Only 10 participants (3%) met the BLIPS criterion alone and 5 (2%) met the GRFD criterion alone.

Of 309 participants, 2 dropped out immediately after initial assessment, and as such transition outcome was obtained from the remaining 307 participants. The follow-up rates every 6 months were as follows:

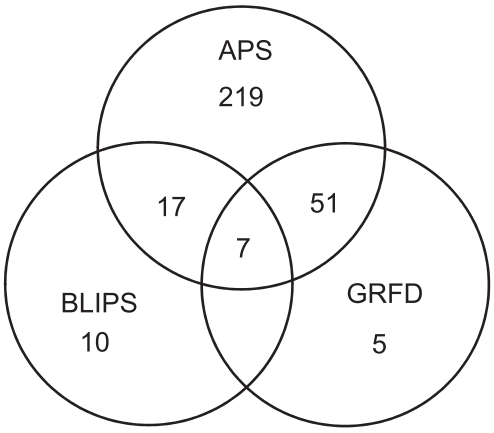

Fig. 2. Venn diagram of the number of patients meeting different criteria for ARMS APS: attenuated positive psychotic symptoms; BLIPS: brief limited intermittent psychotic symptoms; GRFD: genetic risk and functional decline.

77.3% at 6 months, 70.8% at 12 months, 63.5% at 18 months, and 57.3% at 24 months. The mean follow-up duration was 929 days ±782 (median, 752; range, 2–3129) and duration did not different among the three sites (Table 3). One individual was excluded from the study because of methamphetamine abuse.

3.2. Baseline characteristics

Baseline demographic and clinical characteristics are presented in Table 2. We included more female than male participants. Participants had a mean age of 21.4 years, and most were single and living with other people, whereas three-fifths were students. Four participants (1.3%) reported present or past substance use (two with a past history of cannabis use). The average GAF scores indicated that participants generally had severe difficulties with social/role functioning and psychiatric symptoms. When comparing the three sites, the mean age at the Toho site was significantly higher than that at other sites. Because of the difference in age criteria, 5 participants aged between 36 and 40 were included at the Toho site. The mean GAF score was significantly lower at the Tohoku site than at the others. Furthermore, the proportion of married people, employed individuals, and those with a history of psychosis among first-degree relatives also differed among the three sites. Although there was no difference in the results of multiple

Table 2
Socio-demographic and clinical characteristics of the study sample at baseline.

	Toho ($n = 135$)	Tohoku ($n = 118$)	Toyama ($n = 56$)	Total ($n = 309$)	Statistic value	P
Age (mean ± SD, range)	23.4 ± 6.3 (14.3–39.9)	19.8 ± 4.2 (14.2–34.8)	19.7 ± 4.4 (14.2–31.4)	21.4 ± 5.5 (14.2–39.9)	F = 18.0	<0.001[a]
Gender (male/female)	46:89	44:74	29:27	119:190	$X^2 = 5.36$	0.068
Education (mean ± SD, years)	12.3 ± 2.4	11.8 ± 2.3[†]	11.5 ± 2.2	12.0 ± 2.3[†]	F = 2.70	0.069
Married, n (%)	18 (13.3)	6 (5.1)	0 (0.0)	24 (7.8)	$X^2 = 11.7$	0.003
Living with others, n (%)	118 (87.4)	107 (90.7)	51 (91.1)	276 (89.3)	$X^2 = 0.926$	0.629
Students, n (%)	53 (39.3)	91 (77.1)	41 (73.3)	185 (59.9)	$X^2 = 44.2$	<0.001
Employed, n (%)	40 (29.6)	9 (7.6)	8 (14.3)	56 (18.1)		
Unemployed, n (%)	42 (31.1)	18 (15.3)	8 (14.3)	68 (22.0)		
Present/past substance use, n (%)	3 (2.2)	0 (0.0)[§]	1 (1.8)	4 (1.3)[§]	$X^2 = 2.41$	0.299
Present/past cannabis use, n (%)	2 (1.5)	0 (0.0)[§]	0 (0.0)	2 (0.6)[§]	$X^2 = 1.80$	0.407
Past antipsychotic medication, n (%)	28 (21.2)[‡]	47 (39.8)	5 (8.9)	80 (25.9)[‡]	$X^2 = 19.8$	<0.001
First-degree relative with psychotic disorder, n (%)	33 (24.4)	11 (9.3)	0 (0.0)[†]	44 (14.3)[†]	$X^2 = 22.9$	<0.001
GAF (mean ± SD)	52.2 ± 12.9	47.6 ± 7.4	51.1 ± 8.9	50.2 ± 10.6	F = 6.49	.002[b]

GAF: Global Assessment of Functioning.
[†] One participant is missing.
[‡] Three participants are missing.
[§] Seven participants are missing.
[a] Results of a multiple comparison with Toho > Tohoku and Toho > Toyama.
[b] Results of a multiple comparison with Toho > Tohoku and Toyama > Tohoku.

Table 3
Longitudinal follow-up data.

		Toho ($n = 135$)	Tohoku ($n = 117$)	Toyama ($n = 55$)	Total ($n = 307$)
Mean follow-up period (days)		937.7 ± 700.9	958.5 ± 835.4	846.1 ± 857.9	929.2 ± 781.8
Median, days (range)		837 (7–2555)	772 (2–3129)	488 (12–2852)	752 (2–3129)
Transition to psychosis	n (%)	18 (13.3)	16 (13.7)	9 (16.4)	43 (14.0)
	Mean duration to transition (days)	414.2 ± 515.3	344.3 ± 356.6	222.3 ± 204.1	348.0 ± 407.6
	Median (range)	201.5 (14–2067)	251 (8–1376)	144 (13–657)	184 (8–2067)
	Diagnosis after transition	SCZ 16 PD-NOS 1 BDP 1	SCZ 9 SAD 1 DD 1 PD-NOS 5	SCZ 9	SCZ 34 SAD 1 DD 1 PD-NOS 6 BDP 1

SCZ, schizophrenia; SAD, schizoaffective disorder; DD, delusional disorder; PD-NOS, psychotic disorder not otherwise specified; BDP, bipolar disorder with psychotic features.

comparisons, the proportion of first-degree relatives with psychotic disorder were higher at the Toho site. Moreover, 80% of the total sample had a comorbid diagnosis, including 33% with anxiety disorder and 20% with depressive disorder (see Supplemental Table 3).

3.3. Referral source and treatment history

Referral sources varied, with 213 participants (68.9%) referred from a medical doctor, including both psychiatrists ($n = 136$; 44.0%) and non-psychiatrists ($n = 77$; 24.9%), 20 (6.5%) from a school counselor or teacher, and 76 (24.6%) were self-referred. The proportions of each referral source differed among sites (Table 4). There were 80 participants (25.9%) with a history of antipsychotic use and this proportion differed among the sites, with 28 (21.2%) at Toho, 5 (8.9%) at Toyama, and 47 (39.8%) at Tohoku.

3.4. Therapeutic interventions

Therapeutic interventions during follow-up are presented in Table 5. About three-fifths of the total sample were prescribed antipsychotics at least once before transition, and about two-fifths of total sample, including 37 transitioners, were prescribed antipsychotics at the last follow-up point. An eighth of the sample was offered structured CBT. There were differences in the number of participants receiving interventions at each site, including both the prescription of antipsychotics before transition or by the last follow-up, and the provision of structured CBT and day care treatment. In total, 48 participants (15.6%) were admitted to hospital before transition, of whom 14 transitioned during or after hospitalization.

3.5. Transition to psychosis

A total of 43 individuals (14%) developed overt psychosis: 30 (70%) within the first year, seven (16%) in the following year, and six (14%) after two years from enrolment. The mean interval between inclusion and transition was 348 ± 408 days (median, 184; range, 8–2067). Of those who developed psychosis, 34 (79%) were diagnosed with schizophrenia, 6 (14%) with psychotic disorder not otherwise specified, and 3 (7%) with other psychotic disorders, according to the DSM-IV-TR criteria. All transitioned cases met the psychosis criteria of both the CAARMS and the SIPS, except for 2 cases at the Tohoku site. These participants met the psychosis criteria of the CAARMS but not the SIPS because they had >1 week but <4 weeks duration of overt psychotic symptoms. Among participants aged between 36 and 40 at the Toho site, no one showed a transition to psychosis.

With the Kaplan-Meier method, we estimated the cumulative transition rates to psychosis to be 8.8 ± 1.6% at 6 months, 12.0 ± 2.1% at 12 months, 15.7 ± 2.4 at 24 months, 18.8 ± 2.8% at 36 months, and 20.0 ± 3.0% at 48 months (Fig. 3). The log-rank test did not reveal any statistical difference in transition rates among the three sites ($\chi^2 = 1.087$; $P = 0.58$).

The single-variate Cox-regression analyses revealed that only those who met BLIPS criteria showed a higher transition rate to psychosis and no other factors had a significant impact on the transition rate (see Supplemental Table 4). Therefore, we did not perform the planned stepwise Cox-regression analysis.

Table 4
Referral sources.

	Toho ($n = 135$)	Tohoku ($n = 118$)	Toyama ($n = 56$)	Total ($n = 309$)
Self-referral, n (%)	40 (29.6)	15 (12.7)	21 (37.5)	76 (24.6)
School counselor/teacher, n (%)	3 (2.2)	12 (10.2)	5 (8.9)	20 (6.5)
Psychiatrist, n (%)	38 (28.1)	74 (62.7)	24 (42.9)	136 (44.0)
Private outpatient clinic	29	27	12	68
Psychiatric hospital	3	25	2	30
General hospital	6	17	10	33
Student counselors' office	0	5	0	5
Non-psychiatric doctor, n (%)	54 (40.0)	17 (14.4)	6 (10.7)	77 (24.9)
Psychosomatic physician	31	12	1	44
Other	23	5	5	33

4. Discussion

This is the first study to pool data from several specialized ARMS services in Japan to assess transition to psychosis among individuals with ARMS. Our findings suggest that the characteristics of ARMS in this cohort were generally comparable to findings from previous Western and Asian studies despite several differences among sites (see Table 1 and Supplemental Table 1). However, we found several characteristics of this cohort that should be considered when applying the ARMS concept to the local clinical settings.

Although this study was retrospective in design, the sample size was comparable to those of large cohort longitudinal multicenter studies conducted in Europe ($n = 245$) (Ruhrmann et al., 2010) and North America ($n = 291$ in NAPLES 1; $n = 743$ in NAPLES-2) (Cannon et al., 2008; Cannon et al., 2016), and that of single-center studies in Melbourne ($n = 416$) (Nelson et al., 2013) and London ($n = 290$) (Fusar-Poli et al., 2013b). Furthermore, it is the largest longitudinal cohort of individuals with ARMS in Asia.

In this cohort, we observed a transition rate to psychosis of 12% in the first 12 months, 16% in 24 months, 19% in 36 months, and 20% in 48 months. Although these rates are relatively low compared with those reported in a meta-analysis (Fusar-Poli et al., 2012), it has been argued that the transition rate to psychosis in individuals with ARMS has recently declined (Fusar-Poli et al., 2012; Wiltink et al., 2015); therefore, our transition rates are actually within the range in more recent reports (Cannon et al., 2016; Fusar-Poli et al., 2013b). Despite several differences among the three sites, there were no significant differences in the transition rates among sites. These findings suggest that the UHR

Table 5
Type and proportion of therapeutic interventions.

		Toho ($n = 135$)	Tohoku ($n = 117$)	Toyama ($n = 55$)	Total ($n = 307$)	Statistic value	*P*
Antipsychotic medication	At least once before transition, n (%)	115 (85.2)	48 (41.0)	23 (41.8)	186 (60.6)	$\chi^2 = 61.0$	<0.001
	At the last follow-up, n (%) (including transitioners)	72 (53.3)	31 (26.5)	25 (44.5)	128 (41.7)	$\chi^2 = 19.0$	<0.001
Structured CBT	Before transition, n (%)	3 (2.2)	25 (21.4)	11 (20.0)	39 (12.7)	$\chi^2 = 23.9$	<0.001
Day care	Before transition, n (%)	20 (14.8)	2 (1.7)	0 (0.0)	22 (7.1)	$\chi^2 = 21.4$	<0.001
Admission	Before transition, n (%)	27 (20.0)	14 (12.0)	7 (12.7)	48 (15.6)	$\chi^2 = 3.50$	0.174

CBT: cognitive behavioral therapy.

criteria are applicable to specialized service settings in Japan. Although we could not determine which factors actually contributed to the rate of transition in this study, we will discuss clinical characteristics of this cohort.

Previous studies from other Asian regions (Kwon et al., 2012; Lam et al., 2006; Lee et al., 2013; Lim et al., 2015; Liu et al., 2011; Zhang et al., 2014; Zhang et al., 2017) have also confirmed that transition rates to psychosis in Asian samples were within the ranges previously reported in Western samples (Table 1). However, there appears to be some potential differences in transition rates to psychosis among Asian regions. Indeed, the transition rate in the present cohort was lower than that reported in Hong Kong (Lam et al., 2006), Taiwan (Liu et al., 2011), and Shanghai (Zhang et al., 2014; Zhang et al., 2017), but higher than that in Singapore (Lee et al., 2013; Lim et al., 2015) and comparable to that in Seoul (Kwon et al., 2012). Although it is difficult to draw conclusions because of the scarcity of evidence, methodological variabilities across studies (including recruitment method, follow-up period, and treatment strategy during follow-up) and differences in the prevalence of potential risk factors, ARMS might contribute to these differences. More data from diverse regions are necessary to provide evidence for these suggestions.

Consistent with previous studies from Western and Asian regions (Fusar-Poli et al., 2016a; Kwon et al., 2012; Lee et al., 2013; Zhang et al., 2014; Zhang et al., 2017), most participants in the present sample met the APS criterion and few who met the BLIPS or GRFD criterion alone were included. Although the proportion of first-degree relatives with psychotic disorder was higher at the Toho site, most individuals with GRFD also met the APS criterion. Differences in recruitment methods across sites might be responsible for the differences in prevalence of first-degree relatives with a psychotic disorder across sites. Regression analysis revealed that meeting the BLIPS criterion increased the risk of transition to psychosis, whereas genetic risk factors did not, which is also consistent with the results of a recent meta-analysis (Fusar-Poli et al., 2016a). Taken together, the present findings support the notion that clinical guidelines for ARMS should reflect differences in risk levels across subgroups of ARMS (Fusar-Poli et al., 2016a), and GRFD criterion alone should not be viewed as a necessary UHR criterion (Schultze-Lutter et al., 2015).

Although a meta-analysis of outcomes in ARMS suggested that older age is associated with higher risk of transition to psychosis (Fusar-Poli et al., 2012), many studies with samples of children and adults with ARMS have not reported an age effect on future transition to psychosis

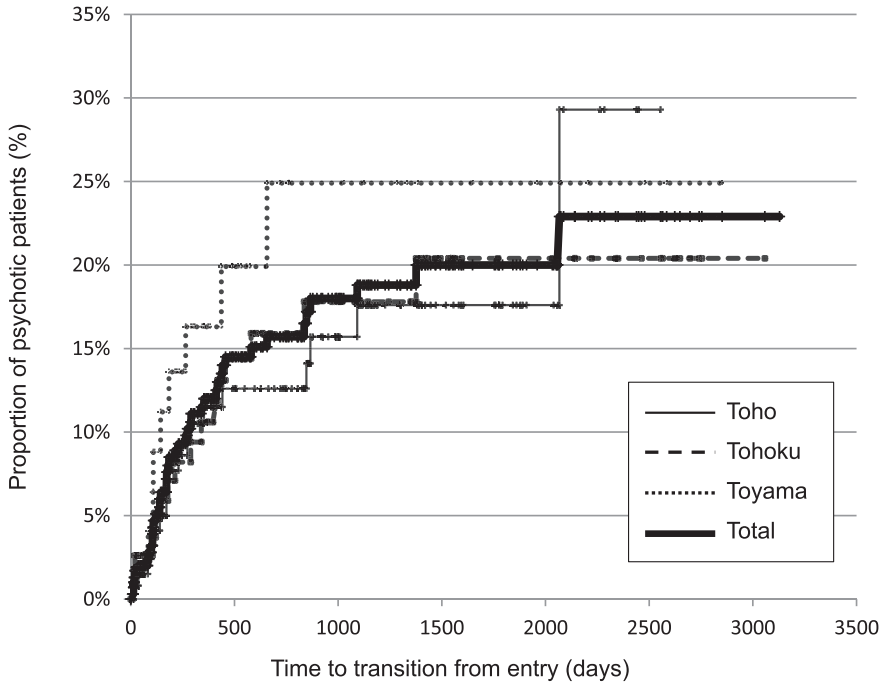

Fig. 3. Kaplan–Meier estimates of the proportion of individuals transitioning to psychosis over time ($N = 307$).

(Buchy et al., 2014; Cannon et al., 2008; Nelson and Yung, 2011; Yung et al., 2004). In accordance with such findings, we observed that the transition rate of children aged between 14 and 17 years did not differ from that of individuals aged 18 or older. Among Asian studies, a study from Shanghai reported that younger individuals with ARMS had higher rates of transition to psychosis (Zhang et al., 2017), whereas a study from Hong Kong (Lam et al., 2006) reported that although they had recruited individuals with ARMS under 12 years old, no children of this age experienced a transition to psychosis during 6-months follow-up. The European Psychiatric Association guidance suggests that transition rates are lower in studies composed of child samples (aged almost entirely ≤18 years) than those in studies composed of more mixed groups (≥50% aged ≤18 years) or adult samples (Schultze-Lutter et al., 2015). However, three of these studies comprising child samples were conducted in non-specialized services, recruiting 285 individuals with ARMS (Lindgren et al., 2014; Manninen et al., 2014; Ziermans et al., 2011), whereas only one study was conducted in a specialized service, recruiting 30 children with ARMS (Welsh and Tiffin, 2014). Resources for child and adolescent mental health might differ between regions and differences in sampling methods between studies may affect age-related characteristics of ARMS, including the transition rate to psychosis. On the basis of the present study, the UHR criteria can be applied to children under 18 in specialized services for ARMS in Japan.

Only one participant was excluded due to substance abuse or dependence and only two individuals had a history of cannabis use. The NAPLE-2 study also excluded individuals with substance-use disorder, observing that 22.0% of their sample reported current use of cannabis (Buchy et al., 2014). Other studies from Western regions have also reported that >30% of individuals with ARMS use cannabis and >18% met the criteria for cannabis use disorder or dependence (Dragt et al., 2012; Phillips et al., 2002). Therefore, our findings suggest a much lower proportion of individuals with ARMS are exposed to cannabis in Asia than are in Western regions (Katsura et al., 2014; Lee et al., 2013; Lee and Kwon, 2016). Use of cannabis is known to increase the risk of schizophrenia (Andreasson et al., 1987; Manrique-Garcia et al., 2012; Murray et al., 2016), and a recent meta-analysis revealed that recurrent use of cannabis might also increase the risk of transition to psychosis in individuals at UHR (Kraan et al., 2016). Therefore, less frequent exposure to cannabis might be responsible for the relatively lower transition rate to psychosis in our cohort. Furthermore, studying ARMS samples from regions with a low prevalence of cannabis use, such as in East Asia, might provide a valuable opportunity to examine the neurobiological and clinical characteristics of ARMS without the influence of cannabis use (Lee and Kwon, 2016).

As with other studies from Asian regions (Kwon et al., 2012; Liu et al., 2011; Zhang et al., 2017), we observed a relatively high rate of antipsychotic prescription in our cohort compared with other large cohort studies in Western regions (see Supplemental Table 1-2). The frequent prescription of antipsychotics during follow-up may be partially explained by the relatively high rate of antipsychotic prescriptions before recruitment. Despite differing prescription rates of antipsychotics among sites, no differences were observed in the transition rates to psychosis among the three sites. Additionally, regression analysis revealed that a prior history of antipsychotic medication was not associated with transition to psychosis. These findings support the notion that antipsychotics are not necessary for most individuals with ARMS and should not be used as a first-line treatment (National Collaborating Centre for Mental Health, 2014; Schmidt et al., 2015). This can avoid the risk of stigmatization, harm to physical health (Foley and Morley, 2011), and potential brain volume reduction (Moncrieff and Leo, 2010). Development of local clinical guidelines and training for clinicians would help to reduce unnecessary prescriptions of antipsychotics to individuals with ARMS in this region.

Few previous studies have reported admission rates for individuals with ARMS. Our results suggest that 15.6% of individuals with ARMS had a severe clinical presentation that needed hospital treatment. Because most individuals with ARMS have comorbid psychiatric disorders and clinical features and the course of ARMS is quite heterogeneous, clinicians should consider the possible need for hospital treatment for ARMS.

Some limitations must be acknowledged in relation to the present study. First, although each site prospectively collected data, the present cohort was retrospectively combined and some important socio-demographic and clinical characteristics for ARMS were not specified in advance. Second, although substantial diagnostic agreement between the CAARMS and SIPS has been demonstrated, slight disagreement between the two instruments has also been reported (Fusar-Poli et al., 2016b). Therefore, future studies adopting the same identification tools across sites are necessary. Third, although we used the Kaplan-Meier method to estimate transition rates to psychosis, increases in the attrition rate over time limits precise calculation of the transition rate of this cohort. Fourth, clinicians involved were recommended to follow international guidelines, individual treatment was not standardized and was customized according to clinical needs. Therefore, it is possible that antipsychotics were prescribed to individuals who were judged by the primary psychiatrists as being at greater risk of developing psychosis (Cornblatt et al., 2007) and we cannot rule out the possibility that this affected the observed transition rate to psychosis. Fifth, although the three centers used the same principal management strategy, potential differences in the specifics of the psychosocial interventions among sites may also have affected the transition rate. Sixth, because we did not assess inter-rater reliability of GAF across sites, the results of GAF should be considered tentative. Lastly, the present data were collected at university hospitals that have specialized services for ARMS, and therefore the generalizability of our findings to more general clinical settings in Japan may be limited. Because of the above-mentioned limitations, our findings should be interpreted cautiously and future prospective studies are necessary to support our conclusions.

Taken together, the present findings support the generalizability of the current concept of ARMS in a non-Western country, Japan. This suggests that recent clinical guidelines for ARMS (National Collaborating Centre for Mental Health, 2014; Schmidt et al., 2015; Schultze-Lutter et al., 2015) may be generally applicable in Japan, at least within specialized services. However, although transition rates did not differ among sites, several differences in clinical services, including referral sources, recruitment and ascertainment methods, and several components of therapeutic interventions, were observed even at specialized services in the same country despite a shared principal management strategy and this might affect some characteristics of sample Therefore, in more general clinical settings, in which resources for services for individuals with ARMS are more limited and most clinicians are not accustomed to the management of ARMS, the generalizability of the present findings may be potentially limited.

To overcome these issues, the development of local clinical guidelines and training for clinicians is necessary to more widely disseminate appropriate management of young individuals with ARMS. In line with this notion, Japanese clinical guidance for early psychosis including ARMS (http://www.jseip.jp/top/document) has been published recently, with funding from the Japan Agency for Medical Research and Development (AMED). The guidance partially incorporates methodology and findings from this study, as well as the evidence developed in the Western countries/settings. Furthermore, training workshops, which was based on this guidance and directed to various people potentially involved in early intervention in mental illness, were held across the country with the grant from the AMED. Further extension of this approach is needed. Finally, Asia is known for its cultural and ethnic diversity and there are numerous differences in mental health systems, including recruitment strategies, access to services, and resources for intervention. There may also be differences in the prevalence of potential risk factors for ARMS among the regions. Therefore, further studies are necessary to apply the ARMS concept to more diverse clinical settings.

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Conflicts of interest

All authors declare no conflicts of interest for the work presented here.

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Appendix A. Supplementary data

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References

Addington, J., Liu, L., Buchy, L., Cadenhead, K.S., Cannon, T.D., Cornblatt, B.A., Perkins, D.O., Seidman, L.J., Tsuang, M.T., Walker, E.F., Woods, S.W., Bearden, C.E., Mathalon, D.H., McGlashan, T.H., 2015. North American Prodrome Longitudinal Study (NAPLS 2): the prodromal symptoms. J. Nerv. Ment. Dis. 203 (5), 328–335.

American Psychiatric Association, 2000. Diagnostic and statistical manual of mental disorders. Text Revision (DSM-IV-TR), fourth ed. Amer Psychiatric Pub Inc., Washington, D.C.

Andreasson, S., Allebeck, P., Engstrom, A., Rydberg, U., 1987. Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. Lancet 2 (8574), 1483–1486.

Buchy, L., Perkins, D., Woods, S.W., Liu, L., Addington, J., 2014. Impact of substance use on conversion to psychosis in youth at clinical high risk of psychosis. Schizophr. Res. 156 (2–3), 277–280.

Cannon, T.D., Cadenhead, K., Cornblatt, B., Woods, S.W., Addington, J., Walker, E., Seidman, L.J., Perkins, D., Tsuang, M., McGlashan, T., Heinssen, R., 2008. Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. Arch. Gen. Psychiatry 65 (1), 28–37.

Cannon, T.D., Yu, C., Addington, J., Bearden, C.E., Cadenhead, K.S., Cornblatt, B.A., Heinssen, R., Jeffries, C.D., Mathalon, D.H., McGlashan, T.H., Perkins, D.O., Seidman, L.J., Tsuang, M.T., Walker, E.F., Woods, S.W., Kattan, M.W., 2016. An individualized risk calculator for research in prodromal psychosis. Am. J. Psychiatry 173 (10), 980–988.

Cornblatt, B.A., Lencz, T., Smith, C.W., Olsen, R., Auther, A.M., Nakayama, E., Lesser, M.L., Tai, J.Y., Shah, M.R., Foley, C.A., Kane, J.M., Correll, C.U., 2007. Can antidepressants be used to treat the schizophrenia prodrome? Results of a prospective, naturalistic treatment study of adolescents. J. Clin. Psychiatry 68 (4), 546–557.

Dragt, S., Nieman, D.H., Schultze-Lutter, F., van der Meer, F., Becker, H., de Haan, L., Dingemans, P.M., Birchwood, M., Patterson, P., Salokangas, R.K., Heinimaa, M., Heinz, A., Juckel, G., Graf von Reventlow, H., French, P., Stevens, H., Ruhrmann, S., Klosterkotter, J., Linszen, D.H., Group, E, 2012. Cannabis use and age at onset of symptoms in subjects at clinical high risk for psychosis. Acta Psychiatr. Scand. 125 (1), 45–53.

Foley, D.L., Morley, K.I., 2011. Systematic review of early cardiometabolic outcomes of the first treated episode of psychosis. Arch. Gen. Psychiatry 68 (6), 609–616.

French, P., Morrison, A.P., 2004. Early Detection and Cognitive Therapy for People at High Risk of Developing Psychosis - a Treatment Approach. John Wiley & Sons, Ltd., Chichester.

Fusar-Poli, P., Bonoldi, I., Yung, A.R., Borgwardt, S., Kempton, M.J., Valmaggia, L., Barale, F., Caverzasi, E., McGuire, P., 2012. Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. Arch. Gen. Psychiatry 69 (3), 220–229.

Fusar-Poli, P., Borgwardt, S., Bechdolf, A., Addington, J., Riecher-Rossler, A., Schultze-Lutter, F., Keshavan, M., Wood, S., Ruhrmann, S., Seidman, L.J., Valmaggia, L., Cannon, T., Velthorst, E., De Haan, L., Cornblatt, B., Bonoldi, I., Birchwood, M., McGlashan, T., Carpenter, W., McGorry, P., Klosterkotter, J., McGuire, P., Yung, A., 2013a. The psychosis high-risk state: a comprehensive state-of-the-art review. JAMA Psychiat. 70 (1), 107–120.

Fusar-Poli, P., Byrne, M., Badger, S., Valmaggia, L.R., McGuire, P.K., 2013b. Outreach and support in South London (OASIS), 2001–2011: ten years of early diagnosis and treatment for young individuals at high clinical risk for psychosis. Eur. Psychiatry 28 (5), 315–326.

Fusar-Poli, P., Cappucciati, M., Borgwardt, S., Woods, S.W., Addington, J., Nelson, B., Nieman, D.H., Stahl, D.R., Rutigliano, G., Riecher-Rossler, A., Simon, A.E., Mizuno, M., Lee, T.Y., Kwon, J.S., Lam, M.M., Perez, J., Keri, S., Amminger, P., Metzler, S., Kawohl, W., Rossler, W., Lee, J., Labad, J., Ziermans, T., An, S.K., Liu, C.C., Woodberry, K.A., Braham, A., Corcoran, C., McGorry, P., Yung, A.R., McGuire, P.K., 2016a. Heterogeneity of psychosis risk within individuals at clinical high risk: a meta-analytical stratification. JAMA Psychiat. 73 (2), 113–120.

Fusar-Poli, P., Cappucciati, M., Rutigliano, G., Lee, T.Y., Beverly, Q., Bonoldi, I., Lelli, J., Kaar, S.J., Gago, E., Rocchetti, M., Patel, R., Bhavsar, V., Tognin, S., Badger, S., Calem, M., Lim, K., Kwon, J.S., Perez, J., McGuire, P., 2016b. Towards a standard psychometric diagnostic interview for subjects at ultra high risk of psychosis: CAARMS versus SIPS. Psychiatry J., 7146341 https://doi.org/10.1155/2016/7146341.

Fusar-Poli, P., Rutigliano, G., Stahl, D., Schmidt, A., Ramella-Cravaro, V., Hitesh, S., McGuire, P., 2016c. Deconstructing pretest risk enrichment to optimize prediction of psychosis in individuals at clinical high risk. JAMA Psychiat. 73 (12), 1260–1267.

Galletly, C., Castle, D., Dark, F., Humberstone, V., Jablensky, A., Killackey, E., Kulkarni, J., McGorry, P., Nielssen, O., Tran, N., 2016. Royal Australian and new Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders. Aust. N. Z. J. Psychiatry 50 (5), 410–472.

International Early Psychosis Association Writing Group, 2005. International clinical practice guidelines for early psychosis. Br. J. Psychiatry Suppl. 48, s120–s124.

Katsura, M., Ohmuro, N., Obara, C., Kikuchi, T., Ito, F., Miyakoshi, T., Matsuoka, H., Matsumoto, K., 2014. A naturalistic longitudinal study of at-risk mental state with a 2.4 year follow-up at a specialized clinic setting in Japan. Schizophr. Res. 158 (1–3), 32–38.

Kobayashi, H., Nozaki, S., Mizuno, M., 2006. Reliability of the structured interview for prodromal syndromes Japanese version (SIPS-J). JPN. J. Soc. Psychiatry 15 (2), 168–174 (in Japanese).

Kobayashi, H., Nemoto, T., Koshikawa, H., Osono, Y., Yamazawa, R., Murakami, M., Kashima, H., Mizuno, M., 2008. A self-reported instrument for prodromal symptoms of psychosis: testing the clinical validity of the PRIME Screen-Revised (PS-R) in a Japanese population. Schizophr. Res. 106 (2–3), 356–362.

Kobayashi, H., Morita, K., Takeshi, K., Koshikawa, H., Yamazawa, R., Kashima, H., Mizuno, M., 2009. Effects of aripiprazole on insight and subjective experience in individuals with an at-risk mental state. J. Clin. Psychopharmacol. 29 (5), 421–425.

Kraan, T., Velthorst, E., Koenders, L., Zwaart, K., Ising, H.K., van den Berg, D., de Haan, L., van der Gaag, M., 2016. Cannabis use and transition to psychosis in individuals at ultra-high risk: review and meta-analysis. Psychol. Med. 46 (4), 673–681.

Kwon, J.S., Byun, M.S., Lee, T.Y., An, S.K., 2012. Early intervention in psychosis: insights from Korea. Asian J. Psychiatr. 5 (1), 98–105.

Lam, M.M., Hung, S.F., Chen, E.Y., 2006. Transition to psychosis: 6-month follow-up of a Chinese high-risk group in Hong Kong. Aust. N. Z. J. Psychiatry 40 (5), 414–420.

Lee, T.Y., Kwon, J.S., 2016. Psychosis research in Asia: advantage from low prevalence of cannabis use. NPJ Schizophr. 2 (1), 1.

Lee, J., Rekhi, G., Mitter, N., Bong, Y.L., Kraus, M.S., Lam, M., Rapisarda, A., Lee, T.S., Subramaniam, M., Chong, S.A., Keefe, R.S., 2013. The Longitudinal Youth at Risk Study (LYRIKS)—an Asian UHR perspective. Schizophr. Res. 151 (1–3), 279–283.

Lim, J., Rekhi, G., Rapisarda, A., Lam, M., Kraus, M., Keefe, R.S., Lee, J., 2015. Impact of psychiatric comorbidity in individuals at ultra high risk of psychosis - findings from the Longitudinal Youth at Risk Study (LYRIKS). Schizophr. Res. 164 (1–3), 8–14.

Lindgren, M., Manninen, M., Kalska, H., Mustonen, U., Laajasalo, T., Moilanen, K., Huttunen, M., Cannon, T.D., Suvisaari, J., Therman, S., 2014. Predicting psychosis in a general adolescent psychiatric sample. Schizophr. Res. 158, 1–6.

Liu, C.C., Lai, M.C., Liu, C.M., Chiu, Y.N., Hsieh, M.H., Hwang, T.J., Chien, Y.L., Chen, W.J., Hua, M.S., Hsiung, P.C., Huang, Y.C., Hwu, H.G., 2011. Follow-up of subjects with suspected pre-psychotic state in Taiwan. Schizophr. Res. 126 (1–3), 65–70.

Manninen, M., Lindgren, M., Therman, S., Huttunen, M., Ebeling, H., Moilanen, I., Suvisaari, J., 2014. Clinical high-risk state does not predict later psychosis in a delinquent adolescent population. Early Interv. Psychiatry 8 (1), 87–90.

Manrique-Garcia, E., Zammit, S., Dalman, C., Hemmingsson, T., Andreasson, S., Allebeck, P., 2012. Cannabis, schizophrenia and other non-affective psychoses: 35 years of follow-up of a population-based cohort. Psychol. Med. 42 (6), 1321–1328.

Matsumoto, K., Ohmuro, N., Tsujino, N., Nishiyama, S., Abe, K., Hmaie, Y., Katsura, M., Inoue, N., Kawasaki, Y., Kishimoto, T., Suzuki, M., Mizuno, M., 2018. An open-label study of cognitive behavioural therapy for individuals with at-risk mental state: feasibility in the Japanese clinical setting. Early Interv. Psychiatry https://doi.org/10.1111/eip.12541 (in press).

McGlashan, T., Walsh, B., Wood, S., 2010. The Psychosis-Risk Syndrome: Handbook for Diagnosis and Follow-up. Oxford University Press, New York.

Miyakoshi, T., Matsumoto, K., Ito, F., Ohmuro, N., Matsuoka, H., 2009. Application of the Comprehensive Assessment of At-Risk Mental States (CAARMS) to the Japanese population: reliability and validity of the Japanese version of the CAARMS. Early Interv. Psychiatry 3, 123–130.

Mizuno, M., Suzuki, M., Matsumoto, K., Murakami, M., Takeshi, K., Miyakoshi, T., Ito, F., Yamazawa, R., Kobayashi, H., Nemoto, T., Kurachi, M., 2009. Clinical practice and research activities for early psychiatric intervention at Japanese leading centres. Early Interv. Psychiatry 3 (1), 5–9.

Mizuno, M., Nemoto, T., Tsujino, N., Funatogawa, T., Takeshi, K., 2012. Early psychosis in Asia: insights from Japan. Asian J. Psychiatr. 5 (1), 93–97.

Moncrieff, J., Leo, J., 2010. A systematic review of the effects of antipsychotic drugs on brain volume. Psychol. Med. 40 (9), 1409–1422.

Morita, K., Kobayashi, H., Takeshi, K., Tsujino, N., Nemoto, T., Mizuno, M., 2014. Poor outcome associated with symptomatic deterioration among help-seeking individuals at risk for psychosis: a naturalistic follow-up study. Early Interv. Psychiatry 8 (1), 24–31.

Murray, R.M., Quigley, H., Quattrone, D., Englund, A., Di Forti, M., 2016. Traditional marijuana, high-potency cannabis and synthetic cannabinoids: increasing risk for psychosis. World Psychiatry 15 (3), 195–204.

National Collaborating Centre for Mental Health, 2014. Psychosis and Schizophrenia in Adults: Prevention and Management. National Institute for Health and Care Excellence, London.

Nelson, B., Yung, A.R., 2011. Ultra high risk (UHR) for psychosis criteria: are there different levels of risk for transition to psychosis? Schizophr. Res. 125, 62–68.

Nelson, B., Yuen, H.P., Wood, S.J., Lin, A., Spiliotacopoulos, D., Bruxner, A., Broussard, C., Simmons, M., Foley, D.L., Brewer, W.J., Francey, S.M., Amminger, G.P., Thompson, A., McGorry, P.D., Yung, A.R., 2013. Long-term follow-up of a Group at Ultra High Risk ("prodromal") for psychosis: the PACE 400 study. JAMA Psychiat. 70 (8), 793–802.

Phillips, L.J., Curry, C., Yung, A.R., Yuen, H.P., Adlard, S., McGorry, P.D., 2002. Cannabis use is not associated with the development of psychosis in an 'ultra' high-risk group. Aust. N. Z. J. Psychiatry 36 (6), 800–806.

Ruhrmann, S., Schultze-Lutter, F., Salokangas, R.K., Heinimaa, M., Linszen, D., Dingemans, P., Birchwood, M., Patterson, P., Juckel, G., Heinz, A., Morrison, A., Lewis, S., von Reventlow, H.G., Klosterkotter, J., 2010. Prediction of psychosis in adolescents and young adults at high risk: results from the prospective European prediction of psychosis study. Arch. Gen. Psychiatry 67 (3), 241–251.

Schmidt, S.J., Schultze-Lutter, F., Schimmelmann, B.G., Maric, N.P., Salokangas, R.K., Riecher-Rossler, A., van der Gaag, M., Meneghelli, A., Nordentoft, M., Marshall, M., Morrison, A., Raballo, A., Klosterkotter, J., Ruhrmann, S., 2015. EPA guidance on the early intervention in clinical high risk states of psychoses. Eur. Psychiatry 30 (3), 388–404.

Schultze-Lutter, F., Michel, C., Schmidt, S.J., Schimmelmann, B.G., Maric, N.P., Salokangas, R.K., Riecher-Rossler, A., van der Gaag, M., Nordentoft, M., Raballo, A., Meneghelli, A., Marshall, M., Morrison, A., Ruhrmann, S., Klosterkotter, J., 2015. EPA guidance on the early detection of clinical high risk states of psychoses. Eur. Psychiatry 30 (3), 405–416.

Tsujino, N., Nemoto, T., Morita, K., Katagiri, N., Ito, S., Mizuno, M., 2013. Long-term efficacy and tolerability of perospirone for young help-seeking people at clinical high risk: a preliminary open trial. Clin. Psychopharmacol. Neurosci. 11 (3), 132–136.

Welsh, P., Tiffin, P.A., 2014. The 'at-risk mental state' for psychosis in adolescents: clinical presentation, transition and remission. Child Psychiatry Hum. Dev. 45 (1), 90–98.

Wiltink, S., Velthorst, E., Nelson, B., McGorry, P.M., Yung, A.R., 2015. Declining transition rates to psychosis: the contribution of potential changes in referral pathways to an ultra-high-risk service. Early Interv. Psychiatry 9 (3), 200–206.

Yung, A.R., Phillips, L.J., McGorry, P.D., McFarlane, C.A., Francey, S., Harrigan, S., Patton, G.C., Jackson, H.J., 1998. Prediction of psychosis. A step towards indicated prevention of schizophrenia. Br. J. Psychiatry Suppl. 172 (33), 14–20.

Yung, A.R., Phillips, L.J., Yuen, H.P., Francey, S.M., McFarlane, C.A., Hallgren, M., McGorry, P.D., 2003. Psychosis prediction: 12-month follow up of a high-risk ("prodromal") group. Schizophr. Res. 60 (1), 21–32.

Yung, A.R., Phillips, L.J., Yuen, H.P., McGorry, P.D., 2004. Risk factors for psychosis in an ultra high-risk group: psychopathology and clinical features. Schizophr. Res. 67, 131–142.

Yung, A., Phillips, L., Simmmons, M.B., Ward, J., Thompson, K., French, P., McGorry, P., 2006. CAARMS (Comprehensive Assessment of at Risk Mental State) Monthly Version 2006. The PACE clinic, Melbourne.

Zhang, T., Li, H., Woodberry, K.A., Seidman, L.J., Zheng, L., Li, H., Zhao, S., Tang, Y., Guo, Q., Lu, X., Zhuo, K., Qian, Z., Chow, A., Li, C., Jiang, K., Xiao, Z., Wang, J., 2014. Prodromal psychosis detection in a counseling center population in China: an epidemiological and clinical study. Schizophr. Res. 152 (2–3), 391–399.

Zhang, T.H., Li, H.J., Woodberry, K.A., Xu, L.H., Tang, Y.Y., Guo, Q., Cui, H.R., Liu, X.H., Chow, A., Li, C.B., Jiang, K.D., Xiao, Z.P., Seidman, L.J., Wang, J.J., 2017. Two-year follow-up of a Chinese sample at clinical high risk for psychosis: timeline of symptoms, help-seeking and conversion. Epidemiol. Psychiatr. Sci. 26 (3), 287–298.

Ziermans, T.B., Schothorst, P.F., Sprong, M., van Engeland, H., 2011. Transition and remission in adolescents at ultra-high risk for psychosis. Schizophr. Res. 126 (1–3), 58–64.