

'A Rose Is a Rose Is a Rose', but At-Risk Criteria Differ

Frauke Schultze-Lutter^a Benno G. Schimmelmann^a Stephan Ruhrmann^b
Chantal Michel^a

^aUniversity Hospital of Child and Adolescence Psychiatry, University of Bern, Bern, Switzerland;

^bDepartment of Psychiatry and Psychotherapy, University of Cologne, Cologne, Germany

Key Words

Psychosis • Early detection • Ultra-high risk • Clinical high risk • Attenuated psychosis syndrome • DSM-5

Abstract

Background: Over the last 15 years, efforts to detect psychoses early in their prodromal states have greatly progressed; meanwhile, ultra-high risk (UHR) criteria have been the subject of such consensus that parts of them have been proposed for inclusion in DSM-5 in terms of an attenuated psychosis syndrome. However, it is frequently unacknowledged that the definitions and operationalizations of UHR-related at-risk criteria, including the relevant attenuated psychotic symptoms, vary considerably across centers and time and, thus, between prediction studies. **Methods:** These variations in UHR criteria are described and discussed with reference to the rates of transition to psychosis, their prevalence in the general population and the proposed new operationalization of the attenuated psychosis syndrome. **Results:** A comparison of samples recruited according to different UHR operationalizations reveals differences in the distribution of UHR criteria and transition rates as well as in the prevalence rates of at-risk criteria in the general population. **Conclusion:** The evidence base for the introduction of such a new syn-

drome is weaker than the number of studies using supposedly equal UHR criteria would at first suggest. Thus, studies comparing the effects of different (sub-)criteria not only on transition rates and outcomes but also on other important aspects, such as neurocognitive performance and brain imaging results, are necessary. Meanwhile, the preliminary attenuated psychosis syndrome in DSM-5 should not follow an altogether new definition but, rather, the currently most reliable UHR definition, which must still demonstrate its reliability and validity outside specialized psychiatric services.

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Introduction

Over the last two decades, the early detection of first-episode psychosis in its initial prodromal state has been given increasing attention, particularly the ultra-high risk (UHR) criteria. The UHR criteria were first proposed and gradually developed thereafter by the Melbourne group of the Personal Assessment and Crisis Evaluation (PACE) clinic [1, 2]. The main aim of the PACE group was the identification of 'people with high likelihood of transition to psychosis within a follow-up period of 12 months' [1]. Their studies resulted in the formulation of three cri-

teria: the attenuated psychotic symptoms (APS), the brief limited intermittent psychotic symptoms (BLIPS), and the trait-state risk factors criterion. Though with different operationalizations, these criteria have since become the most widely used in early detection and at-risk research.

Recently, promising results in first- and second-generation early detection studies have led to the proposal to include a prodromal risk syndrome for first psychosis [3], an APS syndrome [4], and an attenuated psychosis syndrome [5], respectively, in DSM-5, modeled on the APS (online suppl. table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000339208). Drawing on studies of different at-risk samples, Woods et al. [3, 4] argued in their proposal for such a syndrome (1) that the majority of UHR patients present with APS, (2) that patients meeting APS criteria are currently ill through being symptomatic as well as functionally and cognitively impaired and distressed, (3) that these patients are help-seeking, and (4) that they are at high risk of getting worse and/or developing psychosis. In addition, they argued that, compared to help-seeking controls, the higher conversion rates to psychosis in UHR samples signify the sufficient predictive validity of APS in particular [3, 4] and, further, that an excellent interrater reliability for APS has been shown repeatedly. Finally, based on a very small sample of just 30 young volunteers, they argued that clinician-rated APS are infrequent in young people from the general population and that, consequently, a high number of misdiagnoses with such a new syndrome is unlikely [4].

However, these lines of argument do not consider the heterogeneity of UHR (or related) criteria across centers and/or time. This heterogeneity is due to differences in the criteria themselves as well as in their operationalization, as will be outlined in what follows.

UHR and Related Criteria and Their Operationalization

Not only because of their proposed transfer into a DSM-5 diagnosis have APS become the most important of UHR criteria but also because they account for most of the inclusions in UHR studies (online suppl. tables 2–5). Thus, the development of their current definition by the PACE group and their main alternative definition by the Structured Interview for Psychosis-Risk Syndromes (SIPS 5.0) [6] will be described first.

The APS Criteria

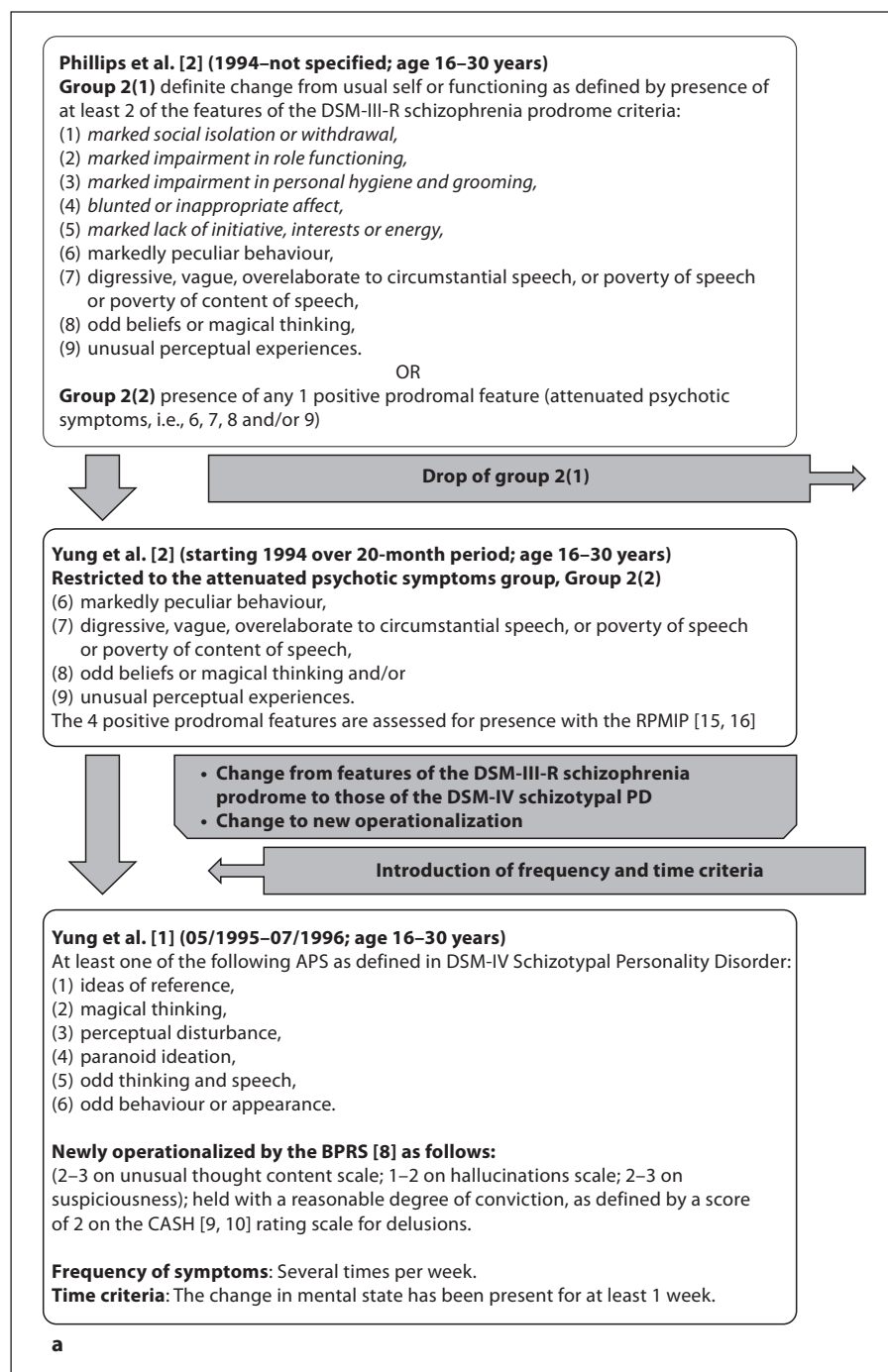
To assess APS, the PACE group first used a broad set of any 2 of the 9 DSM-III-R prodromal symptoms [2] (fig. 1a). This selection was soon narrowed down to at least any 1 of the 4 positive DSM-III-R prodromal symptoms [7] and then to any 1 of the 6 positive DSM-IV schizotypal personality disorder symptoms [1], which were operationalized by the Brief Psychiatric Rating Scale (BPRS) [8] and the Comprehensive Assessment of Symptoms and History (CASH) [9–11] (fig. 1a). Later on, the ‘odd behavior or appearance’ symptom was dropped, and BPRS and CASH were replaced by a gradually developed specialized instrument, the Comprehensive Assessment of at-Risk Mental States (CAARMS) [12, 13] (fig. 1b). Besides symptom assessment, the CAARMS integrates the assessment of all criteria-relevant domains – symptom intensity, frequency, duration, and recency [14]. With the change from BPRS/CASH to CAARMS, very-low-frequency frank psychotic symptoms were removed from the BLIPS definition and added to the APS definition (fig. 1b).

A study of the concurrent validity of the UHR criteria defined by the CAARMS 01/2002 [12] (online suppl. table 2) with the UHR criteria defined by BPRS in a small at-risk sample ($n = 49$) [14] revealed that almost 92% of those who met BPRS-defined criteria also met CAARMS-defined criteria. However, the at-risk status in this sample was defined only by the BPRS. The rate of those positive for the CAARMS-defined but negative for the BPRS-defined UHR criteria therefore remained unknown, which significantly limits the estimation of CAARMS-related effects on risk enrichment in comparison to the BPRS operationalization.

In the latest CAARMS version of 12/2006 [13], a recent significant decline in psychosocial functioning was added as an additional obligate criterion (fig. 1c; table 1), as longitudinal studies had indicated that a decline in functioning indicates a higher risk of transition to psychosis [17, 18].

Based on the PACE UHR criteria and modeled on the Positive and Negative Syndrome Scale (PANSS) [20] and the earliest drafts of the CAARMS, the SIPS, its rating Scale for Prodromal Syndromes, and the Criteria of Prodromal Syndromes (COPS) were developed in the Prevention through Risk Identification, Management and Education (PRIME) clinic [21]. These were recently published as the SIPS 5.0 [6]. With this latest version, a structured rating of additional qualifiers (i.e. symptom onset, symptom worsening, symptom frequency, and symptoms better explained by another axis I disorder) was in-

Fig. 1. Development of the APS criterion by the PACE group over time. **a** From DSM-III-R prodromal symptoms to the first BPRS-based definition. RPMIP = Royal Park Multidiagnostic Instrument for Psychosis.

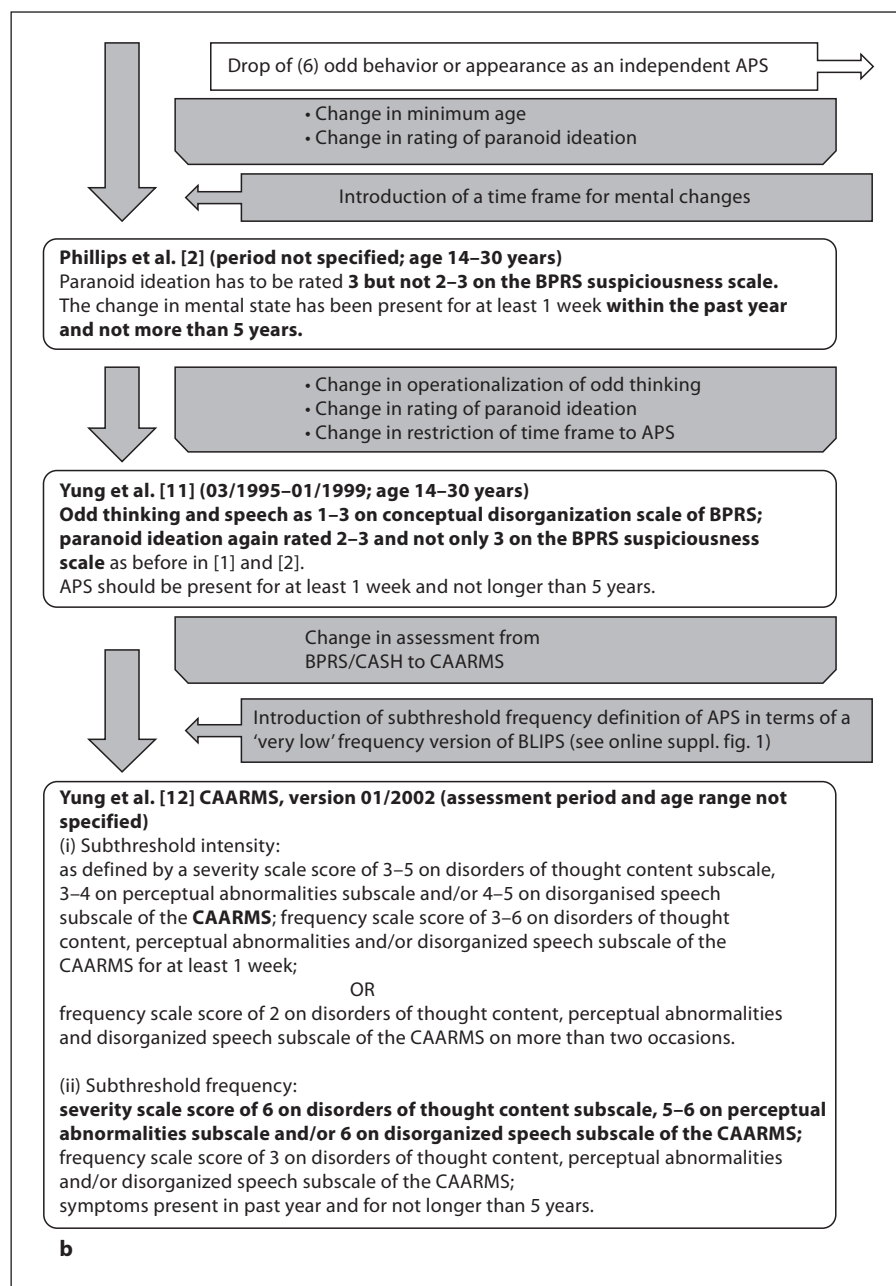


troduced in addition to the original anchor point rating for symptom severity. These qualifiers were already implicit, however, in the rating of the COPS in earlier versions of the SIPS; thus, this introduction of a standardized rating does not constitute a change to the COPS definitions of APS.

Although the PACE UHR operationalizations and COPS were initially developed with close reference to each other, APS definitions differ in some respects.

Differences in the Psychopathological Definitions of APS. While the correspondence between the APS operationalizations by the BPRS and the SIPS is unclear, the

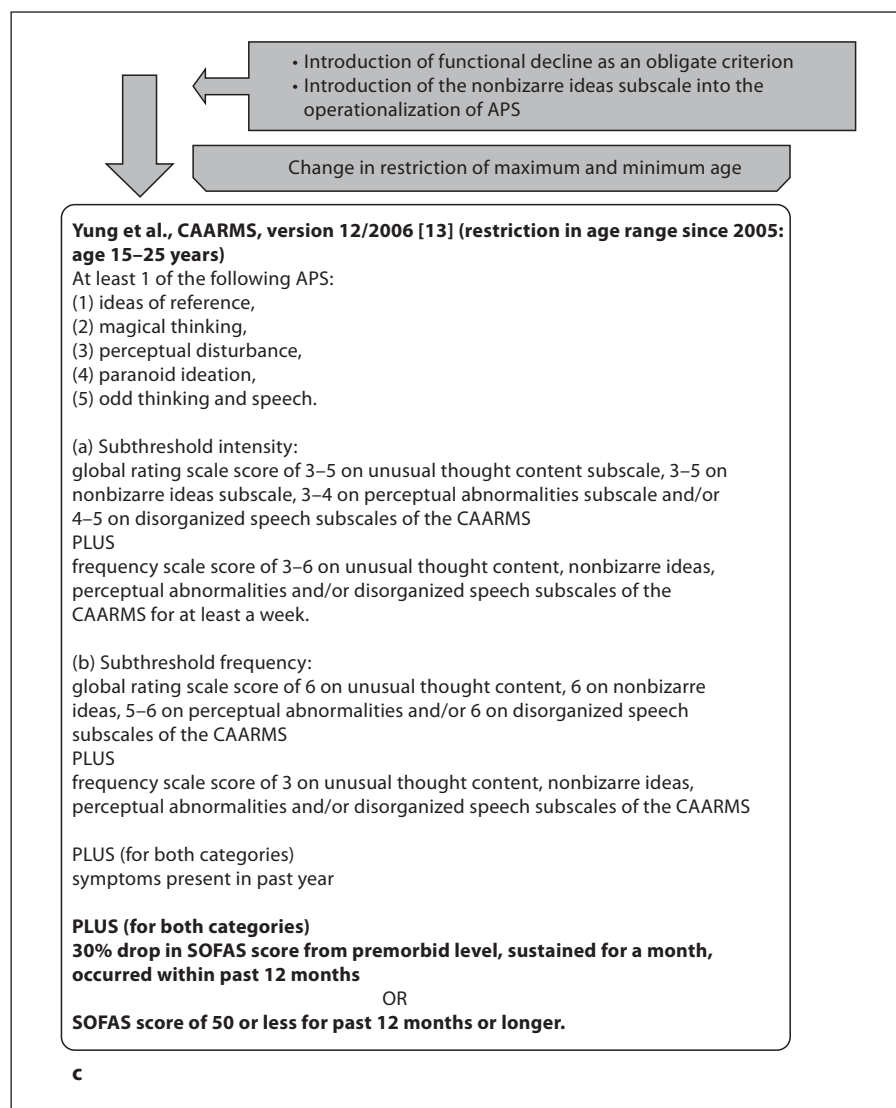
Fig. 1. Development of the APS criterion by the PACE group over time. **b** From BPRS-based definitions to CAARMS-based definitions. CAARMS global rating severity scores: 3 = moderate; 4 = moderately severe; 5 = severe; 6 = psychotic and severe. CAARMS frequency scores: 2 = once a month to twice a week – less than 1 h per occasion; 3 = once a month to twice a week – more than 1 h per occasion OR 3–6 times a week – less than 1 h per occasion; 4 = 3–6 times a week – more than an hour per occasion OR daily – less than an hour per occasion; 5 = daily – more than an hour per occasion OR several times a day; 6 = continuous.



psychopathological differences between CAARMS and SIPS were initially rather insignificant, despite the greater differentiation of 'disorders of thought content' into three subscales in the SIPS (table 1). At least since the CAARMS 2002 version [12, 13], however, 'subthreshold frequency' BLIPS fall into the same category as 'subthreshold intensity' APS (fig. 1b), while all frank psychotic symptoms continue to be rated as BLIPS in the COPS (table 2).

Differences in Time and Frequency Criteria. The PACE UHR criteria and the COPS have always disagreed regarding the maximum duration and occurrence of APS (table 1), with more of an emphasis on recency in the COPS [6, 22], for which APS must have begun or have worsened within the past year and been present for at least once a week in the past month with no restriction on duration for each occurrence. In the CAARMS, meanwhile, with no restriction on general onset or course, APS must have been

Fig. 1. Development of the APS criterion by the PACE group over time. **c** The latest CAARMS 12/2006 definition. SOFAS = Social and Occupational Functioning Assessment Scale. CAARMS global rating severity scores: 3 = moderate; 4 = moderately severe; 5 = severe; 6 = psychotic and severe. CAARMS frequency scores: 2 = once a month to twice a week – less than 1 h per occasion; 3 = once a month to twice a week – more than 1 h per occasion OR 3–6 times a week – less than 1 h per occasion; 4 = 3–6 times a week – more than an hour per occasion OR daily – less than an hour per occasion; 5 = daily – more than an hour per occasion OR several times a day; 6 = continuous.



present in the past year for at least 1 week at a frequency of at least once a month when lasting at least 1 h or a frequency of at least 3 times a week when lasting under 1 h.

Differences in the Functional Decline Criterion. Perhaps the greatest and most influential difference between COPS- and PACE-defined APS was introduced when a significant decline in psychosocial functioning became an obligate criterion of APS (table 1) in the CAARMS 12/2006 [13] (table 1; fig. 1c). The effect of this change on interrater reliability, sample selection (with a potential decrease in sensitivity due to the exclusion of ‘high functioning’ at-risk persons), and transition rate (with a potential increase in specificity through the supposedly stronger risk enrichment) is yet to be seen.

The BLIPS Criteria

The BLIPS criteria were introduced by the PACE group in only the second step of the UHR criteria development [6]. From there, they underwent the same replacement of assessment scales as the APS (online suppl. fig. 1). Furthermore, they were affected by the shift of very-low-frequency frank psychotic symptoms (present in the past year at a frequency of once a month to twice a week when lasting at least 1 h or of 3–6 times a week when lasting less than 1 h) into the APS category [12, 14]. This is different from the COPS, in that all frank psychotic symptoms continue to be rated as BLIPS if psychotic intensity has been reached in the past 3 months (table 2; see also online suppl. fig. 1). Thus, the PACE BLIPS criteria require the

Table 1. Operationalizations of APS by different instruments

	Structured Interview for Prodromal Syndromes and Scale of Prodromal Syndromes (SIPS/SOPS) [6]	Brief Psychiatric Rating Scale (BPRS) [8]	Comprehensive Assessment of At-Risk Mental States (CAARMS 12/2006 version) [13]	Positive and Negative Syndrome Scale (PANSS) [20]
Criteria based on the respective instrument	Criteria of prodromal syndromes (COPS) [6], CARE criteria [19] and EPOS criteria [18]	PACE UHR criteria and FEPSY criteria [35]	PACE UHR criteria (A = subthreshold intensity; B = subthreshold frequency)	PANSS UHR criteria
Unusual thought content/delusional ideas/grandiosity	COPS, CARE and EPOS: P1 and/or P3 score 3–5	PACE: score 2–3 FEPSY: score 3–4	A: score 3–5 B: score 6 on the global rating scale Unusual Thought Content and/or Nonbizarre Ideas	P1- and/or P5-score 3
Suspiciousness/persecutory ideas	COPS, CARE and EPOS: P2 score 3–5	PACE: score 3 FEPSY: score 3–4		P6-score 3–4
Perceptual abnormalities/hallucinations	COPS, CARE and EPOS: P4 score 3–5	PACE: score 1–2 FEPSY: score 2–3	A: score 3–4 B: score 5–6 on the global rating scale Perceptual Abnormalities	P3-score 2–3
Disorganized communication/speech	COPS, CARE and EPOS: P5 score 3–5	PACE: score 1–3 FEPSY: not considered	A: score 4–5 B: score 6 on the global rating scale Disorganised Speech	P2-score 3–4
Disorganized symptoms	CARE: extension of APS to D1–D4 scores 3–5: D1: odd behavior or appearance D2: bizarre thinking D3: trouble with focus and attention D4: personal hygiene/social attentiveness EPOS: extension of APS to D1 score 3–5	–	–	–
General requirements for APS	COPS and EPOS: average frequency of at least once per week in the past month <i>plus</i> development or increase by 1 point in severity within the past year CARE: average frequency of once per month <i>plus</i> symptoms began or worsened in the past year	PACE: frequency of several times per week <i>plus</i> present for at least 1 week within the past year and not more than 5 years FEPSY: frequency of several times per week <i>plus</i> present for at least 1 week	A: score of 3–6 on the respective frequency subscales of the CAARMS for at least a week B: score of 3 on the respective frequency subscale of the CAARMS <i>plus</i> A and B: symptoms present in past year <i>plus</i> New with this version: 30% drop in SOFAS score from premorbid level, sustained for a month, occurred within past 12 months <i>or</i> SOFAS score of 50 or less for past 12 months or longer	Frequency of several times per week <i>plus</i> change in mental state present for 1 week

presence of BLIPS within the past year at a frequency of at least 3–4 times a week when lasting at least 1 h or at least a daily presence when lasting less than 1 h for not more than 1 week (over 1 week being the time threshold of transition criteria). The PACE BLIPS criteria thus allow a longer and more distant presence of frank psychotic symptoms than the COPS do, while requiring a higher minimum frequency. Limiting the onset to the past 3 months, the COPS BLIPS must be present for only at least several minutes per day at a frequency of at least once a month but not more than at least 1 h per day at an average frequency of 4 days per week over 1 month (this is the frequency threshold for transition; table 2). Thus, a subgroup of persons still meeting the BLIPS criteria of the

PACE group would already be considered psychotic using the SIPS, while others would be considered APS by PACE criteria and BLIPS by the COPS.

These differences in frequency, duration, and psychosis threshold might have resulted in a greater proportion of patients with BLIPS in UHR studies using PACE criteria before CAARMS 12/2006. Across studies, the weighted average rate of BLIPS using PACE criteria was 19% [2, 11, 23–26] (see online suppl. tables 1 and 2) compared to 3% in those using COPS [17, 21, 27–31] (see online suppl. tables 3) when weighted for the reported sample size but not controlled for overlapping samples. Thus, one of the arguments advanced by Woods et al. [4] in favor of an attenuated psychosis syndrome – that the ma-

Table 2. Operationalizations of BLIPS by different instruments

	Structured Interview for Prodromal Syndromes and Scale of Prodromal Syndromes (SIPS/SOPS) [6]	Brief Psychiatric Rating Scale (BPRS) [8]	Comprehensive Assessment of At-Risk Mental States (CAARMS 12/2006 version) [13]	Positive and Negative Syndrome Scale (PANSS) [20]
Criteria based on the respective instrument	Criteria of prodromal syndromes (COPS) [6], CARE criteria [19] and EPOS criteria [18]	PACE UHR criteria and FEPSY criteria [35]	PACE UHR criteria	PANSS UHR criteria
Unusual thought content/delusional ideas / grandiosity	COPS, CARE and EPOS: P1 AND/OR P3 score 6	PACE: score ≥ 4 FEPSY: score ≥ 5	score 6 on the global rating scale Unusual Thought Content and/or Nonbizarre Ideas	P1 AND/OR P5 score 4–7
Suspiciousness/persecutory ideas	COPS, CARE and EPOS: P2 score 6	PACE: score ≥ 4 FEPSY: score ≥ 5		P6 score 5–7
Perceptual abnormalities/hallucinations	COPS, CARE and EPOS: P4 score 6	PACE: score ≥ 3 FEPSY: score ≥ 4	score 6 on the global rating scale Perceptual Abnormalities	P3 score 4–7
Disorganized communication/speech	COPS, CARE and EPOS: P5 score 6	PACE: score ≥ 4 FEPSY: score ≥ 5	score 6 on the global rating scale Disorganized Speech	
Disorganized symptoms	CARE: alternatively to P1–P5 scoring of 6 on D1–D4 EPOS: alternatively to P1–P5 scoring of 6 on D1	–	–	–
General requirements for BLIPS	COPS and EPOS: several minutes a day at least 1/month and no more than 1 h a day for 4 days a week (on average) for 1 month <i>plus</i> development within the past 3 months <i>plus</i> symptoms not seriously disorganizing or dangerous CARE: frequency of <1 h and <3–6 times per week or >1 h and ≤ 2 times per week. Each episode of symptoms is present for less than 1 week and spontaneously remits on every occasion. Symptoms began or worsened in the past year	PACE: duration of episode less than a week <i>plus</i> symptoms spontaneously resolve <i>PLUS</i> occurrence within the past year FEPSY: duration of episode less than a week <i>plus</i> symptoms spontaneously resolve	Score of 4–6 on respective frequency subscale of the CAARMS <i>plus</i> each episode of symptoms is present for less than 1 week <i>plus</i> symptoms occurred during last year <i>plus</i> symptoms spontaneously remit on every occasion <i>plus</i> New with this version: 30% drop in SOFAS score from premorbid level, sustained for a month, occurred within past 12 months <i>or</i> SOFAS score of 50 or less for past 12 months or longer	Present for less than 1 week prior to spontaneous resolution

jority of UHR patients would present with APS – seems to apply more to studies using COPS than to those using any of the PACE UHR criteria. However, it is unclear if this proportional difference will remain after the introduction of the additional obligate functional decline criterion in CAARMS 12/2006 (table 2; see also online suppl. fig. 1).

The Trait-State Criterion

The trait-state criterion that generally accounts exclusively for the smallest proportion of at-risk subjects in UHR studies (see online suppl. tables 2–5) has been fairly comparable in the PACE criteria and the COPS after some initial changes in the PACE definitions in the first half of the 1990s (see online suppl. fig. 2). It considers ei-

ther the presence of a 1st-degree relative with psychosis or schizotypal personality disorder of index person as a risk factor that has to be complemented by a significant functional decline (table 3). However, differences emerge in the operationalization of schizotypal personality disorder (with a lower threshold in the SIPS) and of functional decline (table 3).

Other UHR-Related At-Risk Approaches

Additionally to the groups [32, 33] using the PANSS to assess APS and BLIPS (tables 1, 2), other groups have developed variations on the UHR criteria; these will be briefly described below.

Table 3. Operationalizations of ‘trait-state’ risk factor and additional at-risk-criteria by different instruments

	Structured Interview for Prodromal Syndromes and Scale of Prodromal Syndromes (SIPS/SOPS) [6]	Brief Psychiatric Rating Scale (BPRS) [8]	Comprehensive Assessment of At-Risk Mental States (CAARMS 12/2006 version) [13]	Positive and Negative Syndrome Scale (PANSS) [20]
Criteria	Criteria of prodromal syndromes (COPS) [6], CARE criteria [19] and EPOS criteria [18]	PACE UHR criteria and FEPSY criteria [35]	PACE UHR criteria	PANSS UHR criteria
Trait-state risk factor	COPS: 1st-degree relative with any psychotic disorder <i>OR</i> patient has a Schizotypal Personality Disorder acc. to SIPS <i>plus</i> reduction of functioning on the GAF scale of at least 30 % for at least 1 month as compared to 12 months ago CARE: family history of psychosis in 1st-degree relative or schizotypal personality disorder in identified patient. Deterioration in functioning and/or mood, anxiety or deficit symptoms. Symptoms began or worsened in the past year. EPOS: 1st- or 2nd-degree relative with any psychotic disorder <i>or</i> patient has a schizotypal personality disorder acc. to SIPS <i>plus</i> reduction of functioning on the GAF scale of at least 30 % for at least 1 month as compared to highest GAF score ever	PACE: 1st-degree relative with any psychotic disorder <i>or</i> patient has a schizotypal personality disorder acc. to DSM-IV <i>plus</i> reduction of functioning on the GAF scale of at least 30 points from premorbid level for at least 1 month and not more than 5 years FEPSY: 1st- or 2nd-degree relative with a psychotic disorder <i>plus</i> at least 2 of the following risk factors: – ‘kink in the life line’ with a significant decline in functioning over the last 5 years – regular use of cannabis, hallucinogenic drugs, cocaine, amphetamines, inhalations, opioids, phenylcyclidines, or designer drugs within the last 2 years – previous psychiatric disorders or problems – referral for suspected developing psychosis and presence of other prodromal symptoms with onset within the past 2 years	1st-degree relative with any psychotic disorder <i>or</i> patient has a schizotypal personality disorder acc. to DSM-IV <i>plus</i> 30% drop in SOFAS score from premorbid level, sustained for a month, occurred within past 12 months <i>or</i> SOFAS score of 50 or less for past 12 months or longer	Family history of psychosis <i>or</i> patient has a schizotypal personality disorder <i>plus</i> functional deterioration
Additional at-risk criteria	EPOS: COGDIS 2 of 9 cognitive basic symptoms with at least weekly occurrence within the last 3 months: thought interference, blockage or pressure, inability to divide attention, captivation of attention by details of the visual field, disturbances of receptive or expressive speech or abstract thinking, unstable ideas of reference ¹	FEPSY: Nongenetic risk Low number and combination of the 4 above risk factors without family history of psychosis	–	–

¹ As assessed with the Schizophrenia Proneness Instrument, Adult version (SPI-A; Schultze-Lutter F, Addington J, Ruhrmann S, Klosterkötter J. Roma, Giovanni Fioriti Editore s.r.l.; 2007) or Child and Youth Version, Extended English Translation (SPI-CY EET; Schultze-Lutter F, Marshall M, Koch E. Roma, Giovanni Fioriti Editore s.r.l.; 2012, www.fioriti.it).

Clinical High-Risk Criteria

One UHR-related approach to the early detection of schizophrenia was developed by the Hillside Recognition and Prevention program [34], which operates within a child and adolescent psychiatric setting. Dropping the UHR trait-state criterion altogether, the clinical high-risk (CHR) criteria distinguish between 2 at-risk criteria for all psychotic disorders and 1 for schizophrenia as operationalized by the SIPS.

(1) CHR-negative: attenuated negative symptoms; at least any 1 of 6 negative syndrome items of the SIPS with a score of 3–6. The negative, disorganized, and general symptom domains of the SIPS but not its positive domain underwent significant changes between the second and third versions in 2001, changing from a fre-

quency- to a symptom-based severity rating modeled on the anchor point ratings of the positive items. Nevertheless, the SIPS score-based definition of CHR-negative remained the same.

- (2) CHR-positive: APS according to the COPS (table 1); an additional differentiation is possible between moderate APS (with a sum score of all SIPS positive syndrome items of 9 at most) and severe APS (with a sum score of all SIPS positive syndrome items of at least 10).
- (3) Schizophrenia-like psychosis: at least any 1 SIPS positive syndrome item with a score of 6 without meeting the DSM-IV criteria of schizophrenia [e.g. BLIPS (table 2), psychosis not otherwise specified, and brief psychotic episode].

It was hypothesized that schizophrenia would regularly develop from CHR-negative via CHR-positive (i.e. APS and schizophrenia-like psychosis), yet this transition sequence has yet to be demonstrated through sufficiently large samples.

Cognitive Assessment and Risk Evaluation Criteria

The Cognitive Assessment and Risk Evaluation program [19] extended the COPS criteria for APS (table 1) and BLIPS (table 2) by including the 4 items of the SIPS disorganized symptoms dimension. Furthermore, the minimum frequency of APS was reduced from once a week to once a month, and the BLIPS development period was extended from the past 3 months to the past 12 months, thus meeting the time criteria of the PACE BLIPS definition (tables 1, 2).

European Prediction of Psychosis Study Criteria

A similar though less broad extension of the COPS, very close to the earlier PACE definition of APS through 6 schizotypal features (fig. 1a), was made in the European Prediction of Psychosis Study (EPOS) [18]. Therein, APS and BLIPS were alternatively assessed by the SIPS positive items as well as by the 'odd behavior or appearance' (SIPS-D1) item but not by the other 3 disorganized items (tables 1, 2). Moreover, in line with earlier versions of the PACE trait-state criterion (see online suppl. fig. 2), the family risk definition was extended from 1st-degree biological relatives to include the 2nd degree (table 3). A further innovation was that the reference frame for the current Global Assessment of Functioning score was changed from 'highest Global Assessment of Functioning score in the past year' to 'highest Global Assessment of Functioning score ever' (table 3). Last but not least, the EPOS at-risk criteria were supplemented by the basic symptom criterion 'cognitive disturbances' (COGDIS) [18].

'Früherkennung von Psychosen' Criteria

In the Basel 'Früherkennung von Psychosen' (FEPSY) study, the UHR-related FEPSY criteria distinguish not just 3 but 4 at-risk criteria [35]: APS (table 1), BLIPS (table 2), and genetic and nongenetic risk (table 3). As part of a broader assessment instrument [36], APS and BLIPS are defined by the 4 psychosis items of the BPRS. Compared to the BPRS-based definition of the PACE group [1] (tables 1, 2), though, APS and BLIPS (according to the FEPSY study) require a minimum score on the respective BPRS scales that is 1 point higher than required by the PACE criteria. Another innovation concerns the definition of the maximum age for risk, gender-adapted for the

reported gender differences in age of schizophrenia onset: it is set at under 25 years of age for men and under 30 years of age for women [35].

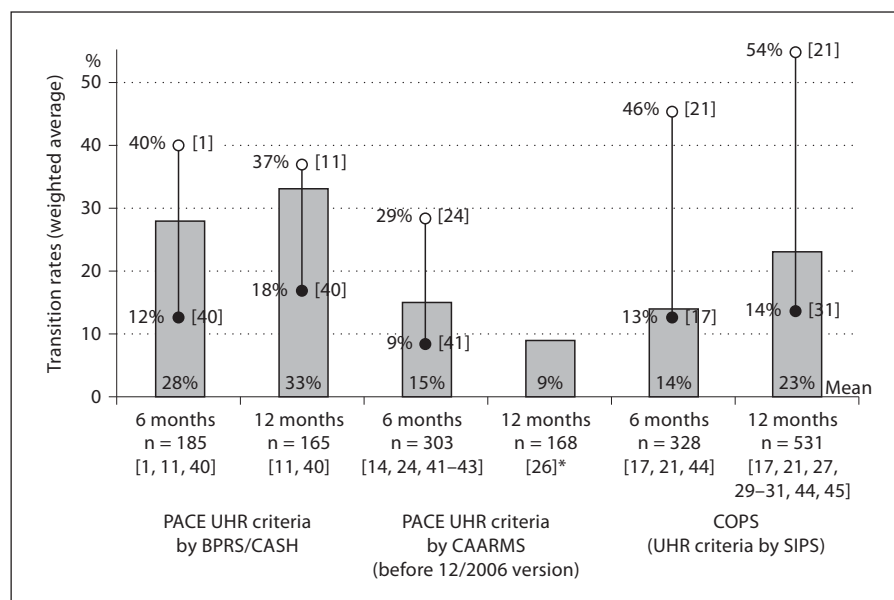
Other approaches relating to the UHR approach but also the basic symptom approach [37] were the risk-state definition of an 'early initial prodromal state' and a 'late initial prodromal state' [38] as well as combinations of the UHR approach and basic symptom criteria, such as in COGDIS [17] and cognitive-perceptive basic symptoms [37]. However, these combinations are generally clearly recognized as deviations from UHR criteria and are therefore not discussed in this paper.

Transition Rates in At-Risk Samples

The degree of variance introduced by the various UHR operationalizations and approaches to transition rates still needs to be examined. That this variance might be significant is indicated by a recent long-term follow-up of participants in PACE studies conducted between 1994 and 2006 [39] that used the UHR criteria valid at the time of intake into the study. Significantly higher transition rates appeared in samples recruited between 1994 and 2000 by intake criteria predominately defined by BPRS than in those recruited between 2001 and 2006 by intake criteria predominately defined by CAARMS (see online suppl. tables 2 and 3). Further analyses revealed that the year of baseline assessment was the strongest predictor of transition [39]. Another difference related to the time of PACE intake and, consequently, UHR criteria definitions concerns the rise in transition rates over time: the 1994 to 1997 cohort showed a fast rise in transition rate that quickly reached a plateau; the 1998 to 2000 cohort initially rose slower but later caught up with the transition rate of the earlier cohort, while the 2001 to 2006 cohort not only had a slower rise than even the 1998 to 2000 cohort but also failed to catch up, remaining significantly lower throughout the follow-up period [39]. The authors advanced sample-related changes as the source of the decrease in transition rates over time (e.g. earlier help-seeking, a dilution of risk by broader help-seeking, or an increase in antipsychotic treatment prior to referral in the more recent samples). However, the possibility that changes in the PACE UHR criteria contributed to this decrease in transition rates awaits close examination [39].

To estimate the potential impact of the UHR operationalizations of PACE and COPS on transition rates to frank psychosis across centers, we compared the published 6- and 12-month transition rates in (sub-)samples

Fig. 2. Mean 6- and 12-month transition rates of the 2 main PACE UHR operationalizations (by BPRS/CASH and by CAARMS) and of COPS, including reported minimum (●) and maximum (○) transition rate. Averages were calculated by weighting for the reported sample sizes; thereby the mean transition rate of each study was multiplied by its respective (sub-)sample size, the resulting products summed up across studies and, finally, divided by the total of sample sizes. * All patients of this study had received some kind of treatment including antipsychotic medication; this might have contributed to the low transition rate.



that were not part of the treatment group of a pharmacological intervention study (fig. 2; see also suppl. tables 2–4 for more detailed study descriptions). Transition rates were weighted for the reported sample size but not controlled for potentially overlapping samples. Consistent with the result of the PACE long-term follow-up [39], figure 2 shows that the greatest difference in average 12-month transition rates occurs between the BPRS- and CAARMS-defined UHR PACE samples, while the COPS samples hold an intermediate position.

Consistent with the findings among the PACE cohort [39], another difference between PACE operationalizations and the COPS seems to concern the lag time to transition and the long-term transition rates. The two large multisample studies of the various PACE criteria [39] and the COPS [17] indicate that the rise in transition rates over time might be steadier when applying the COPS (see online suppl. tables 2–4): while the 2- to 5-year transition rate was already 35% in the COPS sample, it reached 35% only within 10 years in the PACE sample and only 25% within 3 years. As with other sampling effects, this difference might well be related to the more recent onset of at-risk symptoms required by the COPS, lending a greater acuity and progression of symptoms than the PACE UHR criteria.

Studies conducted with other UHR-related at-risk definitions are few, but their mean 12-month transition rates fall within the range reported for the PACE UHR and COPS samples: CHR (only APS: 6%, $n = 48$ [46]), FEPSY

(24%, $n = 50$ [35]), Cognitive Assessment and Risk Evaluation (13%, $n = 48$ [47]), EPOS (14%, $n = 247$ [18, 48]) or UHR by PANSS (35%, $n = 48$ [32–33]) (see online suppl. table 5). Moreover, recent studies combining the UHR and basic symptom approaches indicate that the predictive accuracy of UHR criteria, particularly for APS, might differ depending on the presence of additional subjective cognitive disturbances [18, 37, 48] and that a two-step risk-staging model might be superior to an ‘all-or-nothing’ risk assessment [49]. To this, an attenuated psychosis syndrome could serve as the first, and COGDIS and/or other predictors as the second step.

Psychopathological Significance of At-Risk Criteria

Woods et al. [3, 4] argued in their proposal for an attenuated psychosis syndrome that patients meeting APS criteria are currently ill by being symptomatic, functionally and cognitively impaired, distressed, and help-seeking. These arguments are based, however, on help-seeking clinical samples and are therefore partly circular. Furthermore, using a small nonrepresentative general population sample of 30 young volunteers to assert that APS according to COPS occurred in only 1 (3%), Woods et al. [4] argued that clinician-rated APS are infrequent in young people of the general population and that, consequently, a high number of misdiagnoses of such a new syndrome is unlikely.

Despite some support from other studies, prevalence rates of APS and other at-risk criteria in the general population can be preliminarily estimated from only two studies of similar design that used samples of either insufficient representativeness for the whole age group of at-risk persons [50] or of insufficient size [51]: in a small representative sample of 58 16- to 40-year-olds from the general population, only 1 (2%) met the APS at-risk criteria of the COPS [51]. However, 9 additional persons (16%) reported phenomena that met the psychopathological APS of the SIPS definition but not the frequency and time criteria of the COPS. Furthermore, when the time criteria of the CAARMS (version 01/2002) [12] were applied, the prevalence of at-risk criteria rose to 10% ($n = 6$), while the prevalence decreased to 0% when applying the latest CAARMS (version 12/2006) criteria, including the newly introduced obligate functional decline criterion [13]. Similar findings were reported from a general population sample of 212 11- to 13-year-olds [50]: 8.1% met COPS criteria and 7.7% met APS criteria, although 22.6% reported phenomena in accordance with the psychopathological APS or BLIPS definitions. When applying CAARMS criteria, including the functional decline criterion, the rate of at-risk adolescents dropped to 0.9%. Furthermore, both studies signified that, in the general population, the presence of APS is associated with a greater comorbidity of DSM-IV axis I diagnosis and lower levels of functioning [50, 51] as well as subjective distress related to APS in adolescents [51].

Thus, both studies suggest that APS might have psychopathological significance in themselves while also indicating that APS time criteria and the inclusion or exclusion of psychosocial functioning deficits might play a crucial role beyond the symptom definitions themselves and thus should be considered in the discussion of the psychopathological character of APS in the general population and of the operationalization of a potential attenuated psychosis syndrome in DSM-5, its time and frequency, as well as its progression criteria B and C being currently modeled on the COPS APS criteria (see online suppl. table 1).

These population-related considerations and, consequently, the definition of the new syndrome have major implications [51]. (1) If APS at the population level constitute frequent phenomena of little or no clinical significance (i.e. are not associated with sufficiently poor social functioning and/or distress), a diagnostic category based on APS and related awareness campaigns might do more harm than good by pathologizing nonclinical experiences. In this case and as suggested in criterion D of the pro-

posed attenuated psychotic syndrome (see online suppl. table 1), the inclusion of severe distress, significant disability, or help-seeking as obligatory criteria would be greatly justified. (2) On the other hand, if the prevalence of APS is low and their presence commonly associated with distress and/or certain functional impairments, encouraging help-seeking would be mandatory. In this case, however, the inclusion of the suggested additional higher-threshold qualifiers of criterion D as obligatory diagnostic criteria might prevent the provision of early support before the development of severe distress and/or significant impairments and, consequently, help-seeking.

Conclusion

Over the last 15 years, the body of literature on the early detection of psychosis, particularly in 'UHR samples, has continued to grow and, at first sight, seems to offer solid ground for putting results into clinical practice. However, the differences in the definitions and operationalizations of UHR criteria are frequently missed. Furthermore, it becomes ever harder to perceive which definition of UHR criteria has been used in a UHR study, as a speech confusion in the different suggested denominations and their operationalizations increasingly impedes the comparability of studies [52].

Unrecognized differences in criteria might be an important source of variance across studies regarding not only transition rates but also other psychological and biological parameters studied for their additional psychosis-predictive value or as potential etiological factors in at-risk samples. Thus, advances in scientific and clinical knowledge might be seriously restrained by a failure to account adequately for criteriological variance, particularly as the comparability of studies is further limited by differences in exclusion and transition criteria: for example, substance (mis-)use is an exclusion criterion in SIPS but not in PACE studies, and FEPSY studies using the BPRS require 1 point higher on positive symptom scores for defining transition than PACE studies do (tables 1, 2). Though not discussed in detail here, these differences, particularly in the definition of 'transition', should not be considered less important than the outlined differences in at-risk criteria. Moreover, while we may assume that differences in transition and exclusion criteria might also have contributed to differences in transition rates (just like differences in UHR and related criteria), they have as yet not been considered in discussions on declining tran-

sition rates. Comparative studies of the two most common instruments, SIPS and CAARMS, are still lacking but will, we hope, soon be provided by studies using both [28].

Finally, the completely new operationalization of the currently proposed attenuated psychosis syndrome is unfortunate as, from a strictly methodological point of view, its current instrument-independent operationalization precludes reference to prior findings including prevalence in the general population, associated functional impairment and distress, treatment efficacy and outcome in general beyond conversion rates. Instead of being newly

defined, the definition and operationalization of such a syndrome should therefore follow the most reliable APS operationalization. Comparing at-risk criteria should reveal the most evidence-based operationalization of such a risk syndrome [3, 4] or psychosis spectrum disorder [53, 54], although it would still remain to be shown that the chosen operationalization is also reliable and valid outside scientific and/or specialized psychiatric/psychological frameworks – with no special training in assessment and in general medical practice.

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