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Clinical Validity of *DSM-5* Attenuated Psychosis Syndrome
Advances in Diagnosis, Prognosis, and Treatment

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IMPORTANCE Since the release of the *DSM-5* diagnosis of attenuated psychosis syndrome (*DSM-5*–APS) in 2013, several research studies have investigated its clinical validity. Although critical and narrative reviews have reviewed these progresses, no systematic review has comprehensively summarized the available evidence regarding the clinical validity of *DSM-5*–APS.

OBJECTIVE To provide current evidence on the clinical validity of *DSM-5*–APS, focusing on recent advances in diagnosis, prognosis, and treatment.

EVIDENCE REVIEW A multistep literature search using the Web of Science database, Cochrane Central Register of Reviews, Ovid/PsychINFO, conference proceedings, and trial registries from database inception to June 16, 2019, was conducted following PRISMA and MOOSE guidelines and PROSPERO protocol. Studies with original data investigating individuals diagnosed using *DSM-5*–APS or meeting comparable criteria were included. The results of the systematic review were summarized in tables and narratively synthesized against established evidence-based antecedent, concurrent, and prognostic validators. A quantitative meta-analysis was conducted to explore the cumulative risk of psychosis onset at 6, 12, 24, and 36 months in individuals diagnosed using *DSM-5*–APS criteria.

FINDINGS The systematic review included 56 articles, which reported on 124 validators, including 15 antecedent, 55 concurrent, and 54 prognostic validators. The epidemiological prevalence of the general non–help-seeking young population meeting *DSM-5*–APS criteria was 0.3%; the prevalence of individuals meeting *DSM-5*–APS criteria was variable in clinical samples. The interrater reliability for *DSM-5*–APS criteria was comparable with that of other *DSM-5* mental disorders and can be optimized by the use of specific psychometric instruments. *DSM-5*–APS criteria were associated with frequent depressive comorbid disorders, distress, suicidality, and functional impairment. The meta-analysis included 23 prospective cohort studies, including 2376 individuals. The meta-analytical risk of psychosis onset was 11% at 6 months, 15% at 12 months, 20% at 24 months, and 23% at 36 months. Research into predisposing and precipitating epidemiological factors, neurobiological correlates, and effective treatments for *DSM-5*–APS criteria has been limited.

CONCLUSIONS AND RELEVANCE Over recent years, *DSM-5*–APS criteria have received substantial concurrent and prognostic validation, mostly driven by research into the clinical high-risk state for psychosis. Precipitating and predisposing factors, neurobiological correlates, and effective treatments are undetermined to date.

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Supplemental content

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In 2013, the *DSM-5* introduced the diagnosis of attenuated psychosis syndrome (*DSM-5*–APS) in Research Appendix Section III under the heading Conditions for Further Study.[1(p783)] However, *DSM-5*–APS also appears in the main body of the text,[1(p122)] where it is featured with the official codable diagnosis of other specified schizophrenia spectrum disorder and other psychotic disorder (code 298.8) (eTable 1 in the Supplement).

The rationale for introducing *DSM-5*–APS was grounded in clinical research evidence from the clinical high-risk state for psychosis (CHR-P),[2] which has allowed preventive interventions to enter clinical practice.[3] Consequently, the diagnostic structure of *DSM-5*–APS is based on a subset of CHR-P risk criteria (eAppendix 1 in the Supplement), including the attenuated positive symptom syndrome criteria as defined by the Structured Interview for Psychosis-Risk Syndromes (SIPS-APSS)[4] version 2[5,6] (released June 8, 1998) and, to a lesser extent, the Comprehensive Assessment of At-Risk Mental States[7] operationalization of attenuated psychotic symptoms (CAARMS-APS).

Although the SIPS-APSS, CAARMS-APS, and *DSM-5*–APS criteria all measure attenuated psychotic symptoms, there are substantial operationalization differences across them (**Table 1**). The SIPS-APSS and CAARMS-APS operationalization are measured through semistructured interviews (SIPS and CAARMS, respectively) that require specific psychometric training; conversely, *DSM-5*–APS is unstructured and measured clinically, as any other standard psychiatric diagnosis. Consequently, the interrater agreement is very high within SIPS[10] and CAARMS[11] but lower for *DSM-5*–APS.[12] Psychosis onset is also defined psychometrically under the SIPS-APSS and CAARMS-APS criteria but clinically in *DSM-5*–APS. Another key difference is that while *DSM-5*–APS requires symptoms to be sufficiently distressing and disabling for the patient to warrant clinical attention (criterion D), this is not strictly required by the SIPS-APSS or CAARMS-APS criteria. The CAARMS-APS criteria substantially differ from *DSM-5*–APS with respect to frequency (criterion B) and onset (criterion C) of symptoms, requirements for differential diagnosis with other mental disorders (criterion E; the CAARMS-APS is transdiagnostic[13]), substance misuse (symptoms induced by alcohol and cannabis are included in CAARMS-APS), and threshold of psychosis onset (criterion F; because of different operationalizations of Brief Limited Intermittent Psychotic Symptoms[14,15]).

Since the agreement between *DSM-5*–APS and CAARMS-APS in help-seeking individuals is only moderate,[8] these 2 operationalizations are similar but not identical and cannot be interchangeably used, much like the *DSM-5* schizophrenia and schizophreniform disorders share similarities but are distinctive diagnostic categories. The SIPS-APSS and *DSM-5*–APS criteria are more similar; most patients meeting SIPS-APSS criteria also meet *DSM-5*–APS criteria,[16-19] and most—albeit not all—patients clinically diagnosed using *DSM-5*–APS meet psychometric SIPS-APSS criteria.[16] However, disability and distress (criterion D) are not strictly part of the SIPS-APSS criteria (Table 1); to overcome this discrepancy, SIPS version 5.6 (released May 30, 2014) introduced additional questions to specifically rate criteria A to D of *DSM-5*–APS in addition to the APSS criteria (Table 1). Therefore, only SIPS version 5.6 or likely subsequent editions can be used to psychometrically rate *DSM-5*–APS in a strict sense.

To our knowledge, this is the first systematic review, complemented by meta-analyses, that comprehensively assesses the advancements in diagnosis, prognosis, and treatment specifically for *DSM-5*–APS or closely related criteria. This is opposed to loosely focusing on CHR-P findings that are not directly comparable. This work may inform the revision of the *DSM-5* and future research in the field.

Key Points

Question What is the clinical validity of *DSM-5* attenuated psychosis syndrome (*DSM-5*–APS)?

Findings In this systematic review including 56 articles and meta-analysis including 23 cohort studies, the clinical validity of *DSM-5*–APS was tested against evidence-based antecedent, concurrent, and prognostic validators. *DSM-5*–APS has received substantial concurrent and prognostic validation, mostly from psychometric research in the field of the clinical high-risk state for psychosis, while precipitating and predisposing epidemiological factors, neurobiological research, and treatments have been underinvestigated to date.

Meaning Although current evidence supports the potential clinical validity of *DSM-5*–APS, more research should address the epidemiological profile of this diagnostic category as well as predisposing and precipitating risk factors, neurobiological correlates, and effectiveness of treatments.

Methods

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline (eTable 2 in the Supplement)[20] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guideline (eTable 3 in the Supplement).[21] The study protocol was registered in PROSPERO (CRD42019139330).

Search Strategy and Selection Criteria

A multistep literature search was performed using the following keywords: (*Attenuated Psychosis Syndrome* OR *Attenuated Psychosis Symptoms Syndrome* OR *APS* OR *APSS*). First, the Web of Science database (Clarivate Analytics) was searched, incorporating the Web of Science Core Collection, BIOSIS Citation Index, KCI Korean Journal Database, MEDLINE, Russian Science Citation Index, and SciELO Citation Index, as well as the Cochrane Central Register of Reviews and Ovid/PsychINFO databases from database inception to June 16, 2019, in English. Second, data in relevant conference proceedings (Schizophrenia International Research Society and Early Intervention in Mental Health) and trial registries were searched. Third, the references of systematic reviews or meta-analyses that were retrieved were manually searched.

Abstracts of articles identified that were not relevant were screened out. The remaining full-text articles were then assessed for inclusion eligibility against the inclusion and exclusion criteria.

Condition and Individuals Being Studied

The following inclusion criteria were used: (1) original studies, abstracts, or conference proceedings with no restriction on the topic investigated; (2) conducted in individuals meeting the *DSM-5*–APS, SIPS-APSS, or SIPS version 5.6 operationalization of *DSM-5*–APS criteria (Table 1); and (3) published in English. The following

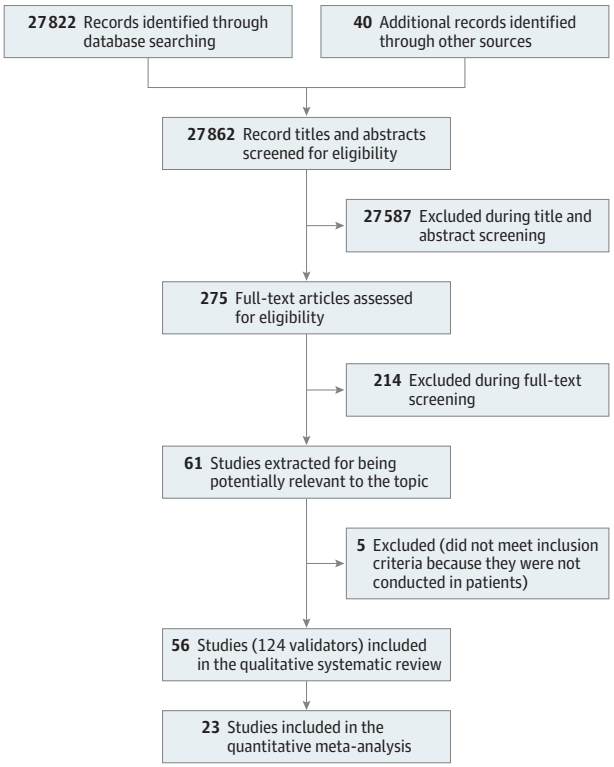
Table 1. Diagnostic Criteria of *DSM-5* Attenuated Psychosis Syndrome (*DSM-5*–APS) Compared With the Attenuated Positive Symptom Syndrome Criteria Defined by the Structured Interview for Psychosis-Risk Syndromes (SIPS-APSS) and Attenuated Psychosis Symptoms Criteria Defined by the Comprehensive Assessment of At-Risk Mental States (CAARMS-APS)

	Criteria; Year of Publication			
Diagnostic Criteria	*DSM-5*–APS[1]; 2013	SIPS-APSS[4-6]; 1998	SIPS Version 5.6 Operationalization of *DSM-5*–APS; 2014	CAARMS-APS[7]; 2006
Severity	Criterion A: at least 1 of the following symptoms is present in attenuated form with relatively intact reality testing and is of sufficient severity or frequency to warrant clinical attention: (1) delusions, (2) hallucinations, and (3) disorganized speech	SIPS positive symptom scales: (P1) unusual thought content, (P2) suspiciousness, (P3) grandiose ideas, (P4) perceptual abnormalities, and (P5) disorganized communication, with at least 1 of these symptoms rated 3, 4, or 5, indicating clinically significant disturbance below a psychotic level of intensity	Same as SIPS-APSS	CAARMS positive symptoms scales rated as 3 to 5 for unusual thought content (P1) and nonbizarre ideas (P2), as 3 to 4 for perceptual abnormalities (P3), and as 4 to 5 for disorganized speech (P4)
Frequency	Criterion B: symptom(s) must have been present at least once per week for the past month	Symptoms ever been present at an average frequency of at least once per week over a month	Same as SIPS-APSS	Symptoms present from once per month to twice per week for >1 h per occasion or 3 to 6 times per week for <1 h per occasion
New onset and worsening	Criterion C: symptom(s) must have begun or worsened in the past year	Symptoms begin within the past year or any symptom currently rated 1 or more scale points higher compared with 12 mo ago; only symptoms that occurred over the past month are rated	Same as SIPS-APSS	Need to be present in the past 12 mo; rated the most severe in the past 12 mo
Distress/disability	Criterion D: symptom(s) is sufficiently distressing and disabling to the individual to warrant clinical attention	Subjective qualifier not used to assign the designation	Attenuated positive symptoms sufficiently distressing and disabling to the patient to warrant clinical attention	Rated on a scale from 0 to 100 but not used to assign the designation
Differential diagnosis	Criterion E: symptom(s) is not better explained by another mental disorder, including a depressive or bipolar disorder with psychotic features, and is not attributable to the physiological effects of a substance or another medical condition	Symptoms ever not been explained better by another *DSM* disorder	Same as SIPS-APSS	No requirement for differential diagnosis with other mental disorders
Lack of lifetime psychotic disorder	Criterion F: criteria for any psychotic disorder have never been met	Severity score of 6 on at least 1 of P1 to P5 and symptoms ever occur for at least 1 h/d at an average frequency of 4 d/wk over 1 mo or symptoms are seriously disorganizing and dangerous (urgency criteria)	Same as SIPS-APSS	Severity score of 6 on at least 1 of P1, P2, and P4 and/or score of 5 to 6 on P3 and frequency of at least 3 to 6 d/wk at >1 h per occasion or daily at <1 h per occasion and symptoms present for longer than 1 week; urgency criteria were not considered
Substance misuse	Assessed within criterion E	Exclude if symptoms are strongly intertwined temporally with substance use episodes	Same as SIPS-APSS	Exclude if symptoms occur only during peak intoxication from hallucinogens, amphetamines, and cocaine; included if due to cannabis or alcohol
Antipsychotic treatments	Not assessed	Usually assessed and considered as an exclusion criterion	Same as SIPS-APSS	Usually assessed and considered as an exclusion criterion
Functional decline	No social/occupational dysfunction decline requirement	No social/occupational dysfunction decline requirement	Same as SIPS-APSS	30% drop in SOFAS score from premorbid level sustained for 1 mo within the past 12 mo or SOFAS score <50 for the past ≥12 mo
Assessment	Unstructured clinical interview	Semistructured psychometric interview	Same as SIPS-APSS	Semistructured psychometric interview
Duration of the assessment	From 20 min[8] to 45 min[9]	Approximately 2 h	Same as SIPS-APSS	Approximately 2 h
Specific psychometric training	Not required	Required	Same as SIPS-APSS	Required

Abbreviation: SOFAS, Social and Occupational Functioning Assessment Scale.

exclusion criteria were used: (1) reviews, editorials, or clinical cases; (2) unpublished data; (3) studies measuring attenuated psychotic symptoms outside the *DSM-5*–APS, SIPS-APSS, or SIPS version 5.6 operationalization of *DSM-5*–APS criteria, such as those using the Basel Screening Instrument for Psychosis[22] or CAARMS-APS,[7] which are prognostically but not diagnostically comparable with *DSM-5*–APS[8]; and (4) studies that do not report specific information on the SIPS-APSS or CAARMS-APS group alone but reported composite results, including other CHR-P subgroups (eg, Brief Limited Intermittent Psychotic Symptoms/Brief Intermittent Psychotic Symptoms and Genetic Risk and Deterioration Syndrome).

Figure 1. PRISMA Flowchart Outlining Study Selection Process



Outcome Measures and Data Extraction

Data were independently extracted by 2 researchers (G.S.P. and A.C.), and discrepancies were resolved consulting a third senior academic (P.F.-P.). The variables extracted included validator (antecedent, concurrent, or prognostic), author and year of publication, study type (original or abstract), study design (cross-sectional, prospective, retrospective, intervention, or naturalistic), type of diagnostic assessment (clinical or psychometric, including the SIPS version, face-to-face evaluation, medical record review, or telephone), diagnostic criteria (*DSM-5*–APS, SIPS-APSS, or SIPS version 5.6 operationalization of *DSM-5*–APS criteria), sample size, mean age and percentage of women, quality assessment, and key findings.

Quality Assessment

Study quality was assessed in all included studies. A modified version of the Newcastle-Ottawa Scale was used for cross-sectional and cohort studies[23,24] (eTable 4 in the Supplement).

Systematic Review

To systematically assess the validity of *DSM-5*–APS, the available evidence was structured in 3 main classes of potential validators, adapted from Kendler[25]:

1. Antecedent validators, including demographic factors and predisposing and precipitating risk factors.
2. Concurrent validators, including diagnostic factors and diagnostic agreement, comorbidity, neurobiological and neurocognitive factors, symptom measures and functioning, and baseline treatments.
3. Prognostic validators, including overall prognostic accuracy, risk of psychosis onset, predictors of outcomes, and response to treatments.

Meta-analysis

A quantitative meta-analysis was conducted to test the risk of psychosis onset using *DSM-5*–APS, SIPS-APSS, or SIPS version 5.6 operationalization of *DSM-5*–APS criteria (Table 1). The risk of psychosis onset was estimated as the proportion of individuals at risk who developed psychotic disorders (using SIPS, *International Classification of Diseases*, or *DSM*) at 6, 12, 24, and 36 or more months of follow-up, updating a previous publication.[26] A secondary meta-analysis was conducted to address the proportion of individuals meeting the *DSM-5*–APS, SIPS-APSS, or SIPS version 5.6 operationalization of *DSM-5*–APS criteria presenting with comorbid mental disorders (using *International Classification of Diseases* or *DSM*). For these meta-analyses, additional inclusion criterion were nonoverlapping samples and availability of at least 3 independent studies reporting on the same outcome. For pooling proportions in a meta-analysis of multiple studies, the metaprop package 21[27] of Stata statistical software version 14 (StataCorp) was used. The 95% CIs were based on score procedures.[26,28] Since high heterogeneity was expected, random-effects meta-analyses were conducted.[29] Publication biases were assessed with the metafunnel[30] and with the Egger test in metabias[31] functions of Stata[32]; the trim-and-fill method was used to correct the estimates in the case of publication biases.[33] Heterogeneity among study point estimates was assessed using Q statistics. The proportion of the total variability in the effect size estimates was evaluated with the I^2 index.[34] Meta-regressions were planned when there was substantial heterogeneity (>50%) and at least 10 studies per each outcome. All *P* values reported in the meta-analysis were 2-sided, and the level of significance was set at a *P* value less than .05.

Results

Database

The literature search yielded 27 852 citations, which were screened for eligibility; 56 articles reporting on 124 validators, including 15 antecedent validators, 55 concurrent validators, and 54 prognostic validators, were included in the systematic review (**Figure 1**). A total of 21 studies (38%) were used for the risk of psychosis meta-analysis, and 10 studies (18%) were used for the risk of comorbid mental disorders meta-analysis. A total of 46 studies (82%) used SIPS-APSS criteria, 5 (9%) used *DSM-5*–APS diagnosis, 5 (9%) used both *DSM-5*–APS and SIPS-APSS criteria (in 1 study,[18] the sample was mixed, and in 4 studies,[17,25-27] the sample met both criteria), and none used SIPS version 5.6 operationalization of *DSM-5*–APS criteria. The total sample sizes in the included studies ranged from 21 individuals[35] to 2101 individuals[36]; the sample sizes in studies with individuals meeting *DSM-5*–APS and SIPS-APSS criteria ranged from 4 individuals[37] to 689 individuals.[38] The age of participants ranged from 14.6 years[39] to 24.8 years.[8] There were 26 studies from the United States, 16 from Europe, 11 from Australasia, and 3 across different countries.

Antecedent Validators

Demographic Factors

The epidemiological prevalence of the general non–help-seeking young population meeting *DSM-5*–APS criteria was 0.3% (eTable 5 in the Supplement).[37] The onset/worsening criterion C excluded 2.3% of the general population who felt distressed by attenuated psychotic symptoms.[37] The prevalence of individuals meeting the SIPS-APSS criteria was 1.3%[40] in the general population and 3.5% in college students.[41] The prevalence of individuals meeting SIPS-APSS criteria in clinical samples was highly variable, ranging from 3.1%[36] to 80%[42]; the association of age with the prevalence of help-seeking individuals meeting *DSM-5*–APS and SIPS-APSS criteria was inconsistent.[39,42,43] Retrospectively, 44% of patients diagnosed as having schizophrenia would have met *DSM-5*–APS criteria in the past.[16]

Predisposing and Precipitating Risk Factors

A total 47.8% of individuals meeting SIPS-APSS criteria reported having experienced at least 1 type of trauma (eTable 5 in the Supplement).[44] Younger individuals aged 15 to 18 years meeting SIPS-APSS criteria had better social and role functioning scores and less depressive symptoms than older individuals.[39] Social dysfunction in those meeting SIPS-APSS criteria was associated with symptoms distress.[10]

Concurrent Validators

Diagnostic Factors and Diagnostic Agreement

Assessors agreed with the criterion standard on the presence or absence of *DSM-5*–APS 70% of the time (κ = 0.34) (eTable 6 in the Supplement).[9] Prescreening tools have robust psychometric properties for recognizing individuals meeting SIPS-APSS criteria.[45] The interrater reliability for *DSM-5*–APS (κ = 0.46) is comparable with that of other *DSM-5* mental disorders.[12] The diagnostic agreement between *DSM-5*–APS and CAARMS-APS is only moderate (κ = 0.59).[8]

Comorbidity

Despite criterion E, among individuals meeting *DSM-5*–APS and SIPS-APSS criteria, 49% presented with comorbid depressive disorders, 22% with bipolar disorder, 38% with anxiety disorders, 9% with generalized anxiety disorder, 13% with obsessive-compulsive disorder, 20% with substance use disorders, 13% with cannabis use disorder, 7% with alcohol use disorder, and 22% with social phobia (eTables 7 and 8 in the Supplement). Other comorbid disorders that were not meta-analyzed because there were less than 3 studies included attention-deficit/hyperactivity disorder,[46,47] oppositional defiant disorders,[18] conduct disorders,[18,39] and posttraumatic stress disorder[43] (eTable 6 in the Supplement). Personality disorder traits were also frequent (57.1%),[18] in particular schizotypal personality disorders (rates varied between 17.0%[39] and 67.8%[19]) and borderline personality traits (42.9%[18]). Across help-seeking individuals assessed for *DSM-5*–APS and SIPS-APSS criteria, lifetime suicidality was more frequent in those meeting *DSM-5*–APS and SIPS-APSS criteria than in those not meeting these criteria[42,43]: approximately 26.3%[48] to 38.9%[18] of the population meeting *DSM-5*–APS and SIPS-APSS criteria experienced at least 1 lifetime suicide attempt, and suicidal ideation reached 77.8%.[18] Individuals meeting SIPS-APSS criteria also experienced an increased risk of violence.[49]

Neurobiological and Neurocognitive Factors

Neurocognition[47,50] (particularly vigilance and processing speed[51]), social cognition,[50] and metacognition[47] (which related to self-disturbances[46]) were impaired in individuals meeting SIPS-APSS criteria compared with controls (eTable 6 in the Supplement). Olfactory deficits in individuals meeting SIPS-APSS criteria were associated with the severity of negative symptoms.[35] Individuals meeting SIPS-APSS criteria displayed enhanced frontotemporal functional brain connectivity[52] and reduced mismatch negativity compared with controls.[53]

Symptom Measures and Functioning

Compared with other help-seeking samples, individuals meeting *DSM-5*–APS and SIPS-APSS criteria were more severely ill,[18,42] depressed,[18] and distressed[36] and had poorer functioning[18,42] (eTable 6 in the Supplement). The severity of attenuated psychotic symptoms (positive, negative, disorganized, and general) was significantly higher among help-seeking individuals meeting SIPS-APSS criteria than in those meeting other attenuated psychotic symptom criteria.[42,43] Attenuated psychotic symptoms were also associated with obsessive-compulsive traits, interpersonal sensitivity, and depression.[41] The most frequent unusual thought contents were being perplexed by reality and having overvalued beliefs.[54] The most frequent perceptual abnormalities were simple auditory[44,54] (typically hearing their own voice with a negative content[54]) or simple visual[44]; tactile, olfactory, or complex perceptual abnormalities were more infrequent. The severity of perceptual abnormalities was also lower in male patients compared with female patients[44] and in those with simple compared with complex perceptual abnormalities.[44] The presence of violence content in attenuated psychotic symptoms was associated with increased anxiety, negative beliefs toward self and others, and bullying.[55]

Baseline Treatments

Baseline treatment exposure ranged from 5.5% to 57.1% for antipsychotic medication[17-19,53,56-62] (mostly atypicals[53,56]), 0% to 38.1% for antidepressants,[17-19,58-63] and 4.0% to 20.8% for a combination of both.[17,19,42,60-62,64] Exposure ranged from 4.3% to 33.3% for mood stabilizers[18,58] and 9.8% to 14.3% for anxiolytics[18,58] and was 4.3% for other psychotropic drugs (eg, methylphenidate, antiepileptics)[42] (eTable 6 in the Supplement).

Prognostic Validators

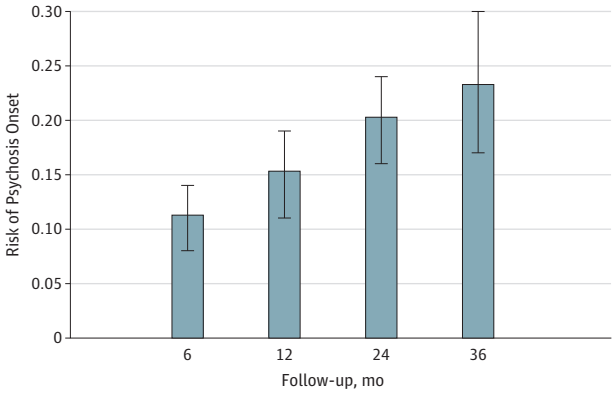
Overall Prognostic Accuracy

There was only 1 study[8] reporting on *DSM-5*–APS prognostic accuracy, which was acceptable at 24 months (area under the curve = 0.76) and comparable with that of CAARMS-APS. Those diagnosed with *DSM-5*–APS had a 5-fold probability of transitioning to psychosis compared with high-risk individuals not diagnosed with *DSM-5*–APS (eTable 9 in the Supplement).[8]

Risk of Psychosis Onset

A total of 23 independent studies (1 using *DSM-5*–APS diagnostic criteria and 22 using SIPS-APSS criteria) reported risk of psychosis onset at follow-up, with an overall sample size of up to 2376 participants. The meta-analytical psychosis risk was 11% at 6 months, 15% at 12 months, 20% at 24 months, and 23% at 36 months follow-up (**Figure 2**) (**Table 2**) (eFigures 1 to 4 in the Supplement). There were publication biases at 12 months and 24 months that were corrected with the trim-

Figure 2. Cumulative Risk of Psychosis Onset Using *DSM-5* Attenuated Psychosis Syndrome or Attenuated Positive Symptom Syndrome Criteria Defined by the Structured Interview for Psychosis-Risk Syndromes



The error bars indicate 95% CIs.

and-fill method (eAppendices 2 to 5 in the Supplement). Meta-regressions did not show any effect of age, sex, publication year, and study quality (eTable 10 in the Supplement). In the only study using *DSM-5*–APS, there was a 28% risk of psychosis at 21 months.[8]

Predictors of Outcomes

Mean age at the time of psychosis onset was 20.3 years for male individuals and 23.5 years for female individuals,[17] with a transition time of 234 days[65] (eTable 9 in the Supplement). Of those who developed psychosis, 64.8% received a diagnosis of schizophrenia using *DSM-5*.[61] A total of 85.1% of individuals reached psychotic intensity on unusual thought content, 43.3% on suspicious ideas, 13.4% on grandiose ideas, and 46.3% on perceptual abnormalities.[65] Psychosis onset was characterized by the presence of Asian or Pacific Islander race,[17] the emergence of new symptoms[65] along with more severe and persisting positive/negative/general symptoms,[17,19,61] and lower subjective well-being.[56,66] Attenuated odd ideas,[17] thought disorder,[17] unusual thought content,[59,61] and auditory perceptual abnormalities[60] were associated with a higher risk of psychosis, while visual perceptual abnormalities were associated with a lower risk.[60] Speech features,[64] in particular disorganized communication,[58,59] were also associated with an increased risk of psychosis as well as a decline in social functioning.[58,59] Verbal memory deficits,[51,58,59] verbal fluency,[59] processing speed,[51,59] and composite cognitive measures[51] were associated with an increased risk of psychosis. Similarly, abnormalities in emotional processing,[45,67] motor dysfunction,[62] olfactory dysfunction,[35] and mismatch negativity[53] were associated with an increased risk of psychosis. Schizotypal personality disorder was not associated with increased risk of psychosis,[19] but axis II disorders along with familial psychiatric history, tobacco use, number of hospitalizations, and history of trauma were associated with suicide attempts.[48] None of these predictors were externally replicated.

Response to Treatment

Naturalistic studies found that 25.5% of individuals received antidepressants for an average of 3 months with no improvement in negative symptoms or social functioning[63] and that 48% of individuals showed little improvement in their symptoms after 1 year, despite being treated with supportive therapy and/or psychotropic medication[56] (eTable 9 in the Supplement). The only available randomized clinical trial[68] found no significant differences in risk of psychosis onset, improvement of severity of symptoms, or functioning between cognitive behavioral therapy and supportive therapy.

Quality Assessment

The Newcastle-Ottawa Scale scores ranged from 3 to 8. The full results are detailed in eTables 11 and 12 in the Supplement.

Discussion

While there are many meta-analyses on CHR-P in the literature, to our knowledge, this is the first systematic review that specifically addressed the clinical validity of *DSM-5*–APS diagnosis or comparable criteria across 56 studies and 124 validators. Most of the evidence reviewed focused on concurrent and prognostic validators in individuals meeting SIPS-APSS criteria, while antecedent factors were rarely investigated.

The systematic review of antecedent validators identified only a few records. The prevalence of individuals meeting *DSM-5*–APS diagnostic criteria is 0.3% in the general population,[37] 3.5% in college students,[41] and highly variable in clinical samples.[8,42,43] The latter point reflects the significant sampling biases that affect the CHR-P paradigm.[69-73] There is an overall paucity of robust epidemiological research addressing the specific risk or protective factors that may exert a predisposing or precipitating role in individuals meeting *DSM-5*–APS and SIPS-APSS criteria. While recent reviews have indicated that psychosis onset is not largely driven by purely genetic risk factors,[23,74,75] it is not clear how these factors accumulate in individuals meeting *DSM-5*–APS and SIPS-APSS criteria. A further public health limitation is that only half of individuals would report a *DSM-5*–APS–like state preceding their first episode of schizophrenia,[16] calling into question the universality of this syndrome as a prepsychotic stage. Other retrospective cohort studies have confirmed a reasonably large subgroup of patients (30%) after the first episode of psychosis for whom there is no evidence of meeting prior CHR-P criteria for any identifiable length of time.[76,77] The possibility that nonpsychotic risk syndromes could precede the first onset of psychosis was summarized in a 2018 systematic review.[78]

The systematic review identified more concurrent validators. Interrater reliability for *DSM-5*–APS is comparable with that of other *DSM-5* mental disorders, although the confidence intervals of the field test were very large.[12] Noticeably, the reliability of *DSM-5*–APS can be optimized if SIPS version 5.6—or subsequent editions—operationalization of *DSM-5*–APS is being used. Unfortunately, to date, only a few studies have acknowledged using this specific SIPS version. Furthermore, despite criterion E requiring a differential diagnosis, half of the individuals meeting *DSM-5*–APS and SIPS-APSS criteria had comorbid major depressive disorders (eTable 8 in the Supplement). This is in line with phenomenological accounts highlighting the role of mood dysregulation during the phases that precede psychosis onset[79] and supporting the notion that psychosis may arise from multiple psychopathological spectra.[80] Given that psychosis onset can occur from nonpsychotic risk syndromes, the removal of this criterion may improve both its prognostic performance and transdiagnostic value.[8,13,81] Symptomatically, individuals meeting *DSM-5*–APS and SIPS-APSS criteria were more severely ill, more depressed, and had poorer functioning than

Table 2. Cumulative Risk of Psychosis Onset in Individuals Meeting *DSM-5* Attenuated Psychosis Syndrome (*DSM-5*–APS) and Attenuated Positive Symptom Syndrome Criteria Defined by the Structured Interview for Psychosis-Risk Syndromes (SIPS-APSS) Criteria

Follow-up, mo	No. of Studies[a]	Individuals Meeting *DSM-5*–APS and SIPS-APSS Criteria, No.	Cumulative Risk of Psychosis (95% CI)	Q	*df*	I^2	*P* Value
6	12	824	0.11 (0.08-0.14)	20.77	11	47.04	.04
12	19	1292	0.15 (0.11-0.19)[b]	61.02	18	72.14	<.001
24	18	2212	0.20 (0.16-0.24)[c]	87.22	17	79.36	<.001
36	7	721	0.23 (0.17-0.30)	22.20	6	72.97	<.001

[a] All studies but one[8] refer to SIPS-APSS.

[b] After using the trim-and-fill method, the cumulative risk of psychosis was 0.10 (95% CI, 0.06-0.15).

[c] After using the trim-and-fill method, the cumulative risk of psychosis was 0.14 (95% CI, 0.10-0.18).

other help-seeking samples not meeting *DSM-5*–APS and SIPS-APSS criteria, with a duration of untreated attenuated psychotic symptoms around 710 days.[26] Attenuated positive psychotic symptoms more frequently included derealization, overvalued beliefs, and simple auditory abnormalities,[44,54] and the presence of violence content was associated with high distress.[55] This supports the notion that *DSM-5*–APS indexes a clinical syndrome, which is disabling per se and independent from the outcomes.[24,81] In fact, most individuals meeting *DSM-5*–APS and SIPS-APSS criteria had suicidal ideation, and up to one-third of them attempted suicide.[18] At baseline, up to 57% of individuals received antipsychotic medication,[18] 38% received antidepressants,[18] and 33% received mood stabilizers,[18] corroborating the polymorbid distressing nature of this syndrome. Neurocognitive,[47,50,51] social cognitive,[50] and metacognitive[47] dysfunction, although not diagnostically required, are also frequent, while neurobiological research into individuals meeting *DSM-5*–APS and SIPS-APSS criteria is too limited to draw reliable conclusions.

The systematic review of prognostic validators confirmed that the prognostic accuracy of *DSM-5*–APS is acceptable (area under the curve = 0.76) at 24 months and comparable with the CAARMS-APS criteria.[8] Individuals meeting *DSM-5*–APS and SIPS-APSS criteria had a 5-fold probability of transitioning to psychosis compared with high-risk individuals not meeting these criteria, with a 23% risk of psychosis at 36 months' follow-up (Figure 2) (Table 2) (eFigure 4 in the Supplement). The only study using *DSM-5*–APS reported a 28% risk of psychosis onset at 21 months.[8] Of those who converted, around two-thirds received a diagnosis of schizophrenia.[61] These findings indicate a substantial risk of progression to psychosis on top of the baseline distressing clinical profile of the syndrome. However, predicting clinical outcomes in this population is currently hampered by the lack of externally validated prognostic models[82]; available models developed with stepwise approaches[58] did not replicate well in external samples.[59] There was very limited evidence relating to effective treatments for individuals meeting *DSM-5*–APS and SIPS-APSS criteria, in line with the current state of knowledge of the CHR-P field.[83] To our knowledge, only 1 randomized clinical trial compared cognitive behavioral therapy with supportive therapy[68] and did not find differences between them. Some trials are ongoing and are addressing the potential effects of treatments on clinical remission and functional outcomes[81] beyond psychosis onset.[84]

The potential clinical validity of *DSM-5*–APS is further confirmed by surveys conducted in the general public and health care professionals (eTable 13 in the Supplement). Most practitioners consider *DSM-5*–APS to constitute a mental disorder[85] in which medication, family involvement, and cognitive coping skills can be helpful.[86] Importantly, in these surveys involving the general public, health care professionals,[87] undergraduates,[88] and college students,[89] the levels of stigma associated with the *DSM-5*–APS and SIPS-APSS criteria were not perceived to be higher than other mental disorders or than other psychoticlike experiences.[87,88]

Box. Evidence-Based Reporting Recommendations for Future Clinical Research on *DSM-5* Attenuated Psychosis Syndrome (*DSM-5*–APS)

1. Test the specific *DSM-5*–APS diagnostic criteria A to F upfront in a standard psychiatric clinical assessment
2. Report the exact number of patients meeting the specific *DSM-5*–APS diagnostic criteria A to F
3. If clinical high-risk state for psychosis instruments are being used, indicate their type and version and stratify the findings across SIPS-APSS/CAARMS-APS, Genetic Risk and Deterioration Syndrome, and Brief Limited Intermittent Psychotic Symptoms/Brief Intermittent Psychotic Syndrome subgroups
4. Preferably use SIPS version 5.6—or subsequent editions—operationalization of *DSM-5*–APS for the psychometric assessment of *DSM-5*–APS; ensure an appropriate training
5. If both clinical *DSM-5*–APS and psychometric SIPS-APSS/CAARMS-APS criteria are tested in the same patients, detail their concordance/discordance

Abbreviations: CAARMS-APS, attenuated psychotic symptoms as defined by the Comprehensive Assessment of At-Risk Mental States; SIPS-APSS, attenuated positive symptom syndrome criteria as defined by the Structured Interview for Psychosis-Risk Syndromes.

Limitations

The main limitation of this review is the scarce amount of evidence on precipitating and predisposing factors, neurobiology, and preventive treatments. A further important limitation is that most studies used the SIPS-APSS designation, which does not exactly match *DSM-5*–APS. For example, some studies measured SIPS-APSS criteria and considered them as *DSM-5*–APS diagnostic criteria without clarifying the SIPS version used[18,35,38-47,49,51-60,62-64,66-68,90-101] or whether the symptoms were distressing and disabling to the patient to warrant clinical attention.[43,102] Therefore, this review supports the clinical utility of SIPS-APSS criteria; since *DSM-5*–APS is most similar, it also supports the clinical utility of *DSM-5*–APS diagnosis. Future studies are required to carefully avoid confusing CHR-P operationalizations with *DSM-5*–APS by testing criteria A to F (Table 1) upfront, either clinically or using SIPS version 5.6—or subsequent editions—operationalization of *DSM-5*–APS (**Box**). Accordingly, the text describing *DSM-5*–APS should be revised for accuracy and consistency with the specific evidence presented here. Most importantly, the revision of *DSM-5*–APS should carefully overcome the

current misleading availability of different specifications across the main text and research appendix (eTable 1 in the Supplement). Because of such inconsistency, individuals at risk of psychosis may be mislabeled under the Other Specified Schizophrenia Spectrum and Other Psychotic Disorder code.[43] Furthermore, with few exceptions,[44,54,55] most studies were carried out in relatively small samples.

Conclusions

Current evidence supports the potential clinical validity of *DSM-5*–APS. However, more research is required to clarify the epidemiological profile of this diagnosis, its predisposing and precipitating risk factors, and neurobiological correlates and to identify effective treatments.

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