



King's Research Portal

DOI:

[10.1001/jamapsychiatry.2019.3561](https://doi.org/10.1001/jamapsychiatry.2019.3561)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Salazar De Pablo, G., Catalan, A., & Fusar-Poli, P. (2019). Clinical Validity of DSM-5 Attenuated Psychosis Syndrome: Advances in Diagnosis, Prognosis, and Treatment. *JAMA Psychiatry*.
<https://doi.org/10.1001/jamapsychiatry.2019.3561>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

DSM-5 ATTENUATED PSYCHOSIS SYNDROME: A SYSTEMATIC REVIEW AND META-ANALYSIS OF THE EVIDENCE

- Advances in diagnosis and treatment review-

Gonzalo Salazar de Pablo^{1,2}, Ana Catalan^{1,3,4,5}, Paolo Fusar-Poli^{1,6,7,8}

Affiliations

¹Early Psychosis: Interventions and Clinical-detection (EPIC) lab, Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK;

²Institute of Psychiatry and Mental Health. Department of Psychiatry, Hospital General Universitario Gregorio Marañón, IISGM, School of Medicine, Universidad Complutense, CIBERSAM, Madrid, Spain;

³Department of Psychiatry, Basurto University Hospital, Bilbao, Spain;

⁴Mental Health Group, BioCruces Health Research Institute. Bizkaia, Spain;

⁵Neuroscience Department, University of the Basque Country UPV/EHU, Leioa, Spain;

⁶OASIS service, South London and Maudsley NHS Foundation Trust, London, UK;

⁷Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy;

⁸National Institute for Health Research, Maudsley Biomedical Research Centre, South London and Maudsley NHS Foundation Trust, London, UK.

Abstract: 349

Text: 3527

Tables: 3

Figures: 2

Endnote reference file: DSM-5-APS.enl

Correspondence to: Dr Paolo Fusar-Poli MD PhD, Department of Psychosis Studies, 5th Floor, Institute of Psychiatry, Psychology & Neuroscience, PO63, 16 De Crespigny Park, SE5 8AF London, UK. E-mail: paolo.fusar-poli@kcl.ac.uk.

Key points

Question: What is the clinical validity of the DSM-5 Attenuated Psychosis Syndrome?

Finding: In this systematic review, the clinical validity of the DSM-5 Attenuated Psychosis Syndrome (DSM-5-APS) was tested against evidence-based validators (antecedent, concurrent and prognostic). 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 under-investigated.

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

ABSTRACT

Importance: Since the release of DSM-5 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 summarised the available evidence regarding the clinical validity of DSM-5-APS.

Objective: This systematic review and meta-analysis provide state-of-the-art evidence on the clinical validity of DSM-5-APS.

Data source: Web of Science database (Clarivate Analytics), Cochrane Central Register of Reviews, Ovid/PsychINFO, conference proceedings and trial registries.

Study selection: A multistep literature search up to 16 June 2019 was conducted following PRISMA and MOOSE guidelines and PROSPERO protocol, to include studies with original data investigating individuals with a DSM-5 APS or comparable designations.

Data extraction and synthesis: The results were summarised in tables and narratively synthesised against established evidence-based validators (antecedent, concurrent and prognostic). A quantitative meta-analysis was conducted to explore the risk of psychosis onset in individuals diagnosed with the DSM-5-APS.

Main outcome(s) and measure(s): For the systematic review: antecedent, concurrent and prognostic validators. For the meta-analysis: cumulative risk of psychosis onset at 6-month, 12-month, 24-month and 36-month.

Results: The systematic review included 56 articles, which reported on 124 validators: 15 antecedents, 55 concurrent and 54 prognostic. The epidemiological prevalence of the DSM-5-APS in the general non-help seeking young population is 0.3%; the prevalence

of the DSM-5-APS is variable in clinical samples. The inter-rater reliability for DSM-5-APS is comparable to that of other DSM-5 mental disorders and can be optimised by the use of specific psychometric instruments. The DSM-5-APS is associated with frequent depressive comorbid disorders, distress, suicidality and functional impairment. Across 23 prospective cohort studies, 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 follow-up. Research into predisposing and precipitating epidemiological factors, neurobiological correlates and effective treatments for DSM-5-APS has been limited.

Conclusions and relevance: Over the recent years the DSM-5-APS has received substantial concurrent and prognostic validation, although mostly driven by research into the clinical high-risk state for psychosis. Precipitating and predisposing factors, neurobiological correlates and effective treatments are undetermined.

Key words: Psychosis, Attenuated Psychosis Syndrome; Attenuated Positive Symptom Syndrome; Schizophrenia; Prevention, Risk.

INTRODUCTION:

Six years ago, the DSM-5 introduced the Attenuated Psychosis Syndrome diagnosis¹ (DSM-5-APS) in the research appendix, Section III under “Conditions for further study”, at page 783¹ (Table 1). However, the DSM-5-APS also appears in the main body of text (page 122), where it is featured with the official codable diagnosis (298.8) of “Other Specified Schizophrenia Spectrum Disorder and Other Psychotic Disorder”¹ (eTable 1). The rationale for introducing the DSM-5-APS was grounded on clinical research evidence from the Clinical High Risk state for Psychosis (CHR-P)², which has allowed preventive interventions to enter clinical practice³. Consequently, the diagnostic structure of the DSM-5-APS is based on a subset of CHR-P risk criteria (eIntroduction): Attenuated Positive Symptom Syndrome (APSS) risk criteria, as defined by the Structured Interview for Psychosis-Risk Syndromes (SIPS⁴, from the second version, dated 8th June 1998^{5,6}, Table 1), and -to a lesser extent- Attenuated Psychotic Symptoms (APS) criteria, as defined by the Comprehensive Assessment of At-Risk Mental States (CAARMS⁷; Table 1).

Although the APSS, APS and DSM-5-APS all measure attenuated psychotic symptoms, there are substantial operationalisation differences across them (Table 1). The APSS and APS are measured through semi-structured interviews (SIPS and CAARMS respectively) that require specific psychometric training; conversely, the DSM-5-APS is unstructured and measured clinically -as for any other standard psychiatric diagnosis-. Consequently, the inter-rater agreement is very high within the SIPS⁸ and CAARMS⁹ but lower for the DSM-5-APS¹⁰. The psychosis onset is also defined psychometrically under the APSS and APS but clinically in the DSM-5-APS. Another key difference is that while the 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 APSS or APS. The APS operationalisation substantially differs from the 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 APS is transdiagnostic¹¹), substance misuse (symptoms induced by alcohol and cannabis are included in the APS) and threshold of psychosis onset (criterion F; because of different operationalisations of BLIPS^{12,13}).

Since the agreement between the DSM-5-APS and the APS in help-seeking individuals is only moderate¹⁴, these two operationalisations are similar but not identical, and they cannot be interchangeably used, as much as the DSM-5 schizophrenia and the DSM-5 schizophreniform disorder share similarities but are distinctive diagnostic categories. The APSS and DSM-5-APS are more similar: all patients with APSS are also meeting DSM-5 APS criteria¹⁵⁻¹⁸ and most -albeit not all- patients with DSM5-APS meet APSS criteria (43/44)¹⁵. However, disability and distress (criterion D) are not strictly part of the APSS (Table 1); to overcome this discrepancy the SIPS version 5.6 (dated 30 May 2014, p.44) has introduced an additional question to additionally rate criterion D of the DSM-5-APS (Table 1). Therefore, the SIPSv5.6.-DSM-5-APS can be used to psychometrically rate the DSM-5-APS.

This is the first systematic review, complemented by meta-analytical analyses, which comprehensively assesses the advancements in diagnosis and treatment specifically for DSM-5-APS or closely related operationalisations, as opposed to loosely focusing on CHR-P findings that are not directly comparable.

METHODS

The study (study protocol registered on PROSPERO (CRD42019139330) was conducted in accordance with Preferred Reporting Items for Systematic Reviews and

Meta-Analyses (PRISMA, eTable 2)¹⁹ and Meta-analysis Of Observational Studies in Epidemiology (MOOSE, eTable 3) guidelines²⁰.

Search strategy and selection criteria

A multi-step literature search was performed using the following keywords: (“Attenuated Psychosis Syndrome” OR “Attenuated Psychosis Symptoms Syndrome” OR “APS” OR “APSS”). First, 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 Cochrane Central Register of Reviews, and Ovid/PsychINFO databases from inception, until 16 June 2019, in English. Second, data in relevant conference proceedings (Schizophrenia International Research Society, Early Intervention in Mental Health) and trial registries (<https://clinicaltrials.gov>) 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 inclusion criteria were: a) original studies, abstracts or conference proceedings with no restriction on the topic investigated; b) conducted in individuals meeting the DSM-5-APS, APSS or SIPSv.5.6-DSM-5-APS criteria (Table 1, the rationale is detailed in the introduction); c) studies published in English.

The exclusion criteria were: a) reviews, editorials or clinical cases; b) unpublished data; c) studies measuring attenuated psychotic symptoms outside the DSM-5-APS, APSS or SIPSv.5.6-DSM-5-APS criteria, such as those employing the Basel Screening Instrument for Psychosis (BSIP²¹) or Comprehensive Assessment of At-Risk Mental States (CAARMS⁷) (which are prognostically¹⁴ but not diagnostically comparable to the DSM-5-

APS); d) studies that do not report specific information on the APSS group alone but reported composite results including other CHR-P subgroups (e.g. BLIPS and Genetic Risk and Deterioration Syndrome, GRD).

Outcome measures and data extraction

Data were independently extracted by two researchers (GSP, AC) and discrepancies were resolved consulting a third senior academic (PFP). The variables extracted included: validator (antecedent, concurrent, prognostic -see below), 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, chart review or telephone), diagnostic operationalisation (DSM-5-APS, APSS or SIPSv.5.6-DSM-5-APS), sample size, mean age and percent of females, quality assessment (see below) and key findings.

Quality assessment

Study quality was assessed using a modified version of the Newcastle-Ottawa Scale (NOS) for cross-sectional and cohort studies^{22,23} (eTable 4).

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 et al²⁴:

1. antecedent validators (demographic factors, predisposing and precipitating risk factors);
2. concurrent validators (diagnostic factors and diagnostic agreement, comorbidity, neurobiological and neurocognitive factors, symptom measures and functioning, baseline treatments);
3. prognostic validators (overall prognostic accuracy, risk of psychosis onset, predictors of outcomes, response to treatments).

Meta-analysis

A quantitative meta-analysis was conducted to test the risk of psychosis onset in DSM-5-APS or APSS or SIPSv5.6-DSM-5-APS (Table 1). The risk of psychosis onset was estimated as the proportion of individuals at-risk who developed psychotic disorders (psychosis onset was defined by the SIPS or ICD/DSM) at 6, 12, 24, 36 (or more) months of follow-up, updating a previous publication²⁵. A secondary meta-analysis was conducted to address the proportion DSM-5-APS, APSS or SIPSv.5.6-DSM-5-APS individuals presenting with (DSM/ICD) comorbid mental disorders. For these meta-analyses, additional inclusion criterion were non-overlapping samples and availability of at least 3 independent studies reporting on the same outcome. For pooling proportions in a meta-analysis of multiple studies metaprop package 21²⁶ of Stata statistical software (StataCorp, version 14) was used. The 95% CIs were based on score procedures^{25,27}. Since high heterogeneity was expected, random-effects meta-analyses were conducted²⁸. Publication biases were assessed with the metafunnel²⁹ and with the Egger test³⁰ in metabias³¹ functions of Stata; the trim and fill method was used to correct the estimates in the case of publication biases³². 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 index³³. Meta-regressions were planned when there was substantial heterogeneity (>50%) and at least 10 studies per each outcome.

RESULTS

Database

The literature search yielded 27852 citations, which were screened for eligibility; 56 articles reporting on 124 validators were included in the systematic review (Figure 1): 15 antecedent validators, 55 concurrent validators and 54 prognostic validators. 21 and 10 of the 56 studies were used for the risk of psychosis and comorbid mental disorders meta-

analyses, respectively. 46 studies employed the APSS designation, 5 the DSM-5-APS, 5 both APSS and DSM-5-APS (in 1 study¹⁷ the sample was mixed and in 4 studies^{16,24,25,26} the sample met both criteria) and none acknowledge using the SIPSv5.6-APS-DSM5. The total sample size of the studies included ranged from 21³⁴ to 2101³⁵ individuals; the DSM-5-APS/APSS sample size ranged from 4³⁶ to 689³⁷ and the age of participants ranged from 14.6³⁸ to 24.8¹⁴. There were 26 studies from the US, 16 from Europe, 11 from Australasia and 3 across different countries.

Antecedent validators

Demographic factors

The epidemiological prevalence of the DSM-5-APS in the general non-help seeking young population is 0.3%³⁶ (eTable 5a). The onset/worsening criterion C excluded 2.3% of the general population who felt distressed by attenuated psychotic symptoms³⁶. The prevalence of the APSS is 1.3%³⁹ in the general population and 3.5% in college students⁴⁰. The prevalence of APSS in clinical samples was highly variable ranging from 3.1%³⁵ to 80%⁴¹; the effect of age on the prevalence of DSM-5-APS/APSS in help-seeking samples was inconsistent^{38,41,42}.

Retrospectively, 44% of patients diagnosed with schizophrenia would have met DSM-5-APS criteria in the past¹⁵.

Predisposing and precipitating risk factors

47.8% of APSS individuals reported having experienced at least one type of trauma (eTable 5b)⁴³. Younger APSS individuals (15-18 years) have better social and role functioning scores, less depressive symptoms than the older individuals³⁸. Social dysfunction in APSS is associated with symptoms distress⁸.

Concurrent validators

Diagnostic factors and diagnostic agreement

Assessors agree with the gold standard on the presence or absence of DSM-5-APS 70% (kappa= 0.34), of the times⁴⁴ (eTable 6a). Pre-screening tools have robust psychometric properties for recognising APSS⁴⁵. The inter-rater reliability for DSM-5-APS (kappa= 0.46) is comparable to that of other DSM-5 mental disorders¹⁰. As noted in the introduction, the diagnostic agreement between the DSM-5-APS and the CAARMS 12/2006 is only moderate (kappa= 0.59)¹⁴.

Comorbidity

Despite criterion E, about half (49%) of DSM-5-APS/APSS individuals presented with comorbid depressive disorders, 22% with bipolar disorder, 38% with anxiety disorders, 9% with generalised anxiety disorder, 13% with obsessive-compulsive disorder, 20% with substance use disorders, 13% with cannabis abuse, 7% with alcohol abuse and 22% with social phobia (meta-analytical results are reported in eTable 7-8). Other comorbid disorders that were not meta-analysed because there were less than 3 studies included attention deficit hyperactivity disorder^{46,47}, oppositional defiant disorders¹⁷, conduct disorders^{17,38} and posttraumatic stress disorder (eTable 6b)⁴². Personality disorder traits were also frequent (57.1%)¹⁷, in particular schizotypal personality disorders (rates varied between 17.0%³⁸ and 67.8%¹⁸) and borderline personality traits (42.9%¹⁷). Lifetime suicidality was more frequent in DSM-5-APS/APSS than non-DSM-5-APS/APSS help-seeking individuals^{41,42}: about 26.3%⁴⁸-38.9%¹⁷ of the DSM-5-APS/APSS population suffered at least one lifetime suicide attempt and suicidal ideation reached 77.8%¹⁷. The APSS designation was also associated with an increased risk of violence⁴⁹.

Neurobiological and neurocognitive factors

Neurocognition^{47,50} (particularly vigilance and processing speed⁵¹), social cognition⁵⁰ and

metacognition⁴⁷ (which related to self-disturbances⁴⁶) were impaired in APSS subjects compared to controls (eTable 6c). Olfactory deficits in APSS individuals were associated with the severity of negative symptoms³⁴. APSS individuals displayed enhanced fronto-temporal functional brain connectivity⁵² and reduced mismatch negativity compared to controls⁵³.

Symptom measures and functioning

Compared to other help-seeking samples, DSM-5-APS/APSS individuals were more severely ill^{17,41}, depressed¹⁷, distressed³⁵ and with a poorer functioning^{17,41} (eTable 6d). The severity of attenuated psychotic (positive, negative, disorganised and general) symptoms was significantly higher in APSS than non-APSS help-seeking individuals^{41,42}; attenuated psychotic symptoms were also associated with obsessive-compulsive traits, interpersonal sensitivity and depression⁴⁰. The most frequent unusual thought contents were being perplexed by reality and having overvalued beliefs⁵⁴. The most frequent perceptual abnormalities were simple auditory^{43,54} (typically hearing their own voice with a negative content⁵⁴) or simple visual⁴³; tactile, olfactory or complex perceptual abnormalities were more infrequent. The severity of perceptual abnormalities was also lower in males compared to females⁴³ and in those with simple compared to complex perceptual abnormalities⁴³. The presence of violence content in attenuated psychotic symptoms was associated with increased anxiety, negative beliefs towards self and others and bullying⁵⁵.

Baseline treatments

Baseline treatment exposure was: 5.5% - 57.1 % for antipsychotic medication^{16-18,53,56-62} (mostly atypicals^{53,56}), 0.0%-38.1 for antidepressants^{16-18,58-63} and 4.0%-20.8% for a combination of both^{16,18,41,60-62,64}, 4.3%-33.3% for mood stabilisers^{17,58}, 9.8%-14.3% for anxiolytics^{17,58}, and 4.3% for other psychotropic drugs (methylphenidate, antiepileptics)⁴¹ (eTable 6e).

Prognostic validators

Overall prognostic accuracy

There was only one study reporting on DSM-5-APS prognostic accuracy which resulted acceptable (AUC=0.76) at 24 months and comparable to that of the CAARMS¹⁴; those meeting DSM-5-APS criteria had a 5-fold probability of transitioning to psychosis compared to those high-risk individuals not meeting DSM-5-APS criteria (eTable 9)¹⁴.

Risk of psychosis onset

23 independent studies (1 in DSM-5-APS and 22 in APSS) 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 six months, 15% at 12 months, 20% at 24 months and 23% at 36 months follow-up (Figure 2, Table 2 and eTables 10-13). There were publication biases at 12-month and 24-month that were corrected with the trim and fill method (Table 3 and eTables 14-17). Meta-regressions did not show any effect of age, gender, publication year and study quality (eTable 18). In the only study employing DSM-5-APS, there was a 28% risk of psychosis at 21-month¹⁴.

Predictors of outcomes

Mean age at the time of psychosis onset was 20.3 years for males and 23.5 years for females¹⁶, with a transition time of 234 days⁶⁵ (eTable 9b). Of those who developed psychosis, 64.8% received a diagnosis of DSM schizophrenia⁶¹. 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 abnormalities⁶⁵. Psychosis onset was characterised by the presence of Asian or Pacific Islander race¹⁶, and the emergence of new symptoms⁶⁵ along with more severe and persisting positive/negative/general^{16,18,61} symptoms, and lower subjective well-being^{56,66}.

Attenuated odd ideas¹⁶, thought disorder¹⁶, unusual thought content^{59,61} and auditory perceptual abnormalities⁶⁰ were associated with a higher risk for psychosis, while visual perceptual abnormalities with a lower risk⁶⁰. Speech features⁶⁴, 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^{51,59,58}, verbal fluency⁵⁹, processing speed^{51,59} and composite cognitive measures⁵¹ were associated with an increased risk of psychosis. Similarly, abnormalities in emotional processing^{45,67}, motor dysfunction⁶², olfactory dysfunction³⁴ and mismatch negativity⁵³ were associated with an increased risk of psychosis. Schizotypal personality disorder was not associated with increased risk of psychosis¹⁸ but axis II disorders along with familial psychiatric history, tobacco use, number of hospitalisations, history of trauma were associated with suicide attempts⁴⁸. None of these predictors was externally replicated.

Response to treatment

Naturalistic studies found that 25.5% of individuals received antidepressants for an average of 3-month with no improvement in negative symptoms or social functioning⁶³ and that 48% of individuals showed little improvement in their symptoms, after one year, despite being treated with supportive therapy and/or psychotropic medication⁵⁶ (eTable 9d). The only available randomised controlled trial found no significant differences in risk of psychosis onset, improvement of severity of symptoms or functioning between cognitive behavioural therapy and supportive therapy⁶⁸.

Quality assessment

The NOS scores ranged from 3 to 8 (eTables 19-20).

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 across 56 studies and 124 validators. Most of the evidence reviewed focused on concurrent and prognostic validators in APSS individuals, while antecedent factors were rarely investigated.

The systematic review of antecedent validators identified only a few records. The prevalence of DSM-5-APS is 0.3% in the general population³⁶, 3.5% in college students⁴⁰ and highly variable in clinical samples^{14,41,42}. The latter point reflects the significant sampling biases that affect the CHR-P/APSS paradigm⁶⁹⁻⁷³. 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 the DSM-5-APS/APSS. While recent reviews have indicated that psychosis onset is largely driven by non-purely genetic risk factors^{74,75,22}, it is not clear how these factors accumulate in DSM-5-APS/APSS samples. A further public health limitation is that only half of individuals would report a DSM-5-APS like state preceding their first episode of schizophrenia¹⁵, questioning the universality of this syndrome as pre-psychotic stage. Other retrospective cohort studies have confirmed a reasonably large subgroup (30%) of first episode of psychosis patients for whom there is no evidence of meeting prior CHR-P criteria for any identifiable length of time^{76,77}. The possibility that non-psychotic risk syndromes could precede the first onset of psychosis was recently summarised at meta-analytical level⁷⁸.

The systematic review identified more concurrent validators. Inter-rater reliability for DSM-5-APS is comparable to that of other DSM-5 mental disorders, although the confidence intervals of the field test were very large¹⁰. Noticeably, the reliability of the DSM-5-APS can be optimised if the SIPSv5.6 is being used. Unfortunately, to date, only a few studies have acknowledged using this specific SIPS version. Furthermore, despite the criterion E requiring a differential diagnosis, half of the individuals meeting DSM-5-

APS/APSS had comorbid major depressive disorders (table 2). This is in line with phenomenological accounts highlighting the role of mood dysregulation during the phases that precede the psychosis onset⁷⁹ and supporting the notion that psychosis may arise from multiple psychopathological spectra⁸⁰. Given that psychosis onset can occur from non-psychotic risk syndromes, the removal of this criterion may improve both its prognostic performance and transdiagnostic value^{11,14,81}. Symptomatically, the DSM-5-APS/APSS individuals were more severely ill, more depressed and with a poorer functioning than other help-seeking samples not meeting the DSM-5-APS/APSS, with a duration of untreated attenuated psychotic symptoms was around 710 days²⁵. Attenuated positive psychotic symptoms more frequently included derealisation, overvalued beliefs and simple auditory abnormalities^{43,54} and the presence of violence content was associated with high distress⁵⁵. This supports the notion that DSM-5-APS indexes a clinical syndrome which is disabling per se and independent from the outcomes^{23,81}. In fact, the vast majority of DSM-5-APS/APSS individuals had suicidal ideation and up to one-third of them attempted suicide¹⁷. At baseline, up to 57% of individuals received antipsychotic medication¹⁷, 38% antidepressants¹⁷ and 33% mood stabilisers¹⁷, corroborating the polymorbid distressing nature of this syndrome. Neurocognitive^{47,50,51}, social cognitive⁵⁰ and metacognitive⁴⁷ dysfunction, although not diagnostically required, are also frequent, while neurobiological research into DSM-5-APS/APSS is too limited to draw reliable conclusions.

The systematic review of prognostic validators confirmed that DSM-5 APS prognostic accuracy is acceptable (AUC=0.76) at 24 months and comparable to the CAARMS¹⁴. Individuals meeting DSM-5 APS/APSS criteria had a 5-fold probability of transitioning to psychosis compared to those high-risk individuals not meeting these criteria, with a 23% risk of psychosis at 36 months follow-up (Figure 2, Table 2 and eTable 13). The only study employing DSM-5-APS criteria reported a 28% risk of psychosis onset at 21-month¹⁴. Of those who converted, around 2/3 received a diagnosis of schizophrenia⁶¹.

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 models⁸²; available models developed with stepwise approaches⁵⁸ did not replicate well in external samples⁵⁹. There was very limited evidence relating to effective treatments for DSM-5-APS/APSS, in line with the current state of knowledge of the CHR-P field⁸³. Only one randomised controlled trial compared cognitive behavioural therapy and supportive therapy without finding differences between them⁶⁸. Some trials are ongoing and are addressing the potential effects of treatments on clinical remission and functional outcomes⁸¹ beyond psychosis onset⁸⁴.

The potential clinical validity of DSM-5-APS is further confirmed by surveys conducted in the general public and health care professionals (eTable 21). Most practitioners consider DSM-5-APS to constitute a mental disorder⁹⁸ in which medication, family involvement and cognitive coping skills can be helpful⁹⁹. Importantly, in none of these surveys involving the general public, health care professionals¹⁰⁰, undergraduates¹⁰¹ and college students¹⁰², the levels of stigma associated with the DSM-5-APS /APSS were perceived higher than other mental disorders or than other psychotic-like experiences^{100,101}.

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 the vast majority of studies employed the APSS designation which does not exactly match the DSM-5-APS. For example, some studies measured APSS and considered them as DSM-5-APS without clarifying the SIPS version used^{17,34,37-43,45-47,49,51-60,62-64,66-68,85-96} or whether the symptoms were distressing and disabling to the patient to warrant clinical attention^{42,97}. Therefore, this review supports the clinical utility of the APSS and since the DSM-5 APS is most similar, it is supporting the DSM-5 APS

clinical utility. Future studies are required to carefully avoid confusing CHR-P operationalisations with the DSM-5-APS category, by testing all the criteria A to F (Table 1) upfront, either clinically or using the SIPSv.5.6-DSM-5-APS (Table 3). Accordingly, the text describing the DSM-5-APS should be revised for accuracy and consistency with the specific evidence presented here. Most importantly, the revision of the DSM-5-APS should carefully overcome the current misleading availability of different specifications across the main text and research appendix (eTable 1). Because of such inconsistency, individuals at risk of psychosis may be mislabelled under the rubric of “Other Specified Schizophrenia Spectrum and Other Psychotic Disorder”⁴². Furthermore, with few exceptions^{43,54,55}, most studies were carried out in relatively small samples.

CONCLUSIONS

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

Funding sources

G.S.P is supported by the Alicia Koplowitz Foundation. P.F.P is supported by PSYSCAN “Translating neuroimaging findings from research into clinical practice”, [EC - European Commission](#). The funders had no influence in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Acknowledgements

The authors declare that there are no conflicts of interest in relation to the subject of this study. G.S. P had full access to all the data in the study and takes responsibility for the

integrity of the data and the accuracy of the data analysis. We are grateful to prof. Scott Woods for his external advice on the APSS versions of the SIPS.

Table 1. DSM-5-APS Attenuated Psychosis Syndrome diagnostic criteria compared with SIPS and CAARMS operationalisations.

	DSM-5-APS (2013)¹	APSS SIPS (from 1998 onwards)⁴⁻⁶	SIPSV.5.6-DSM-5-APS (2014)	CAARMS APS (12/2006)⁷
Diagnostic criteria				
<i>Severity</i>	A. At least one 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 3. Disorganised speech	SOPS-positive symptom scales P1. unusual thought content, P2. suspiciousness, P3. grandiose ideas, P4. perceptual abnormalities, P5. disorganised communication, with at least one of these symptoms rated 3, 4, or 5 indicating clinically significant disturbance below a psychotic level of intensity	As for APSS	CARMS-positive symptoms scales rated 3-5 (P1. unusual thought content, P2. non-bizarre ideas), 3-4 (P3. perceptual abnormalities), 4-5 (P4. disorganised speech)
<i>Frequency</i>	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/week over a month	As for APSS	Symptoms present from 1/month to 2/week, >1 h per occasion, OR 3 to 6/week, <1 h per occasion
<i>New onset and worsening</i>	C. Symptom(s) must have begun or worsened in the past year	Begin within the past year, or any currently rate one or more scale points higher compared to 12 months ago; rated only symptoms that occurred over the past month	As for APSS	Need to be present in the past 12 months; rated the most severe in the past 12 months
<i>Distress/disability</i>	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 0-100 but not used to assign the designation
<i>Differential diagnosis</i>	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	As for APSS	No requirement for differential diagnosis with other mental disorders

<i>Lack of lifetime psychotic disorder</i>	F. Criteria for any psychotic disorder have never been met	Severity score of 6 on at least one of P1–P5 AND symptoms ever occur for at least 1h/day at an average frequency of four days/week over one month OR symptoms are seriously disorganising and dangerous (urgency criteria)	As for APSS	Severity score of 6 on at least one of P1, P2, P4 and/or 5–6 on P3 AND frequency of at least 3 to 6/week, > 1 h per occasion, or daily, <1 h per occasion AND symptoms present for longer than one week. Urgency criteria not considered.
Substance misuse	Assessed within criterion E	Exclude if symptoms are strongly intertwined temporally with substance use episodes	As for 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	As for APSS	Usually assessed and considered as an exclusion criterion
Functional decline	No social/occupational dysfunction decline requirement	No social/occupational dysfunction decline requirement	As for APSS	30% drop in SOFAS score from premorbid level, sustained for a month, within the past 12mo OR SOFAS score <50 for the past 12 months or more
Assessment	Unstructured clinical interview	Semi-structured psychometric interview	As for APSS	Semi-structured psychometric interview
Duration of the assessment	From 20 ¹⁴ to 45 ⁴⁴	About 2 hours	As for APSS	About 2 hours
Specific psychometric training	Not required	Required	As for APSS	Required

*SOFAS: Social and Occupational Functioning Assessment Scale.

Figure 1. PRISMA flowchart outlining study selection process

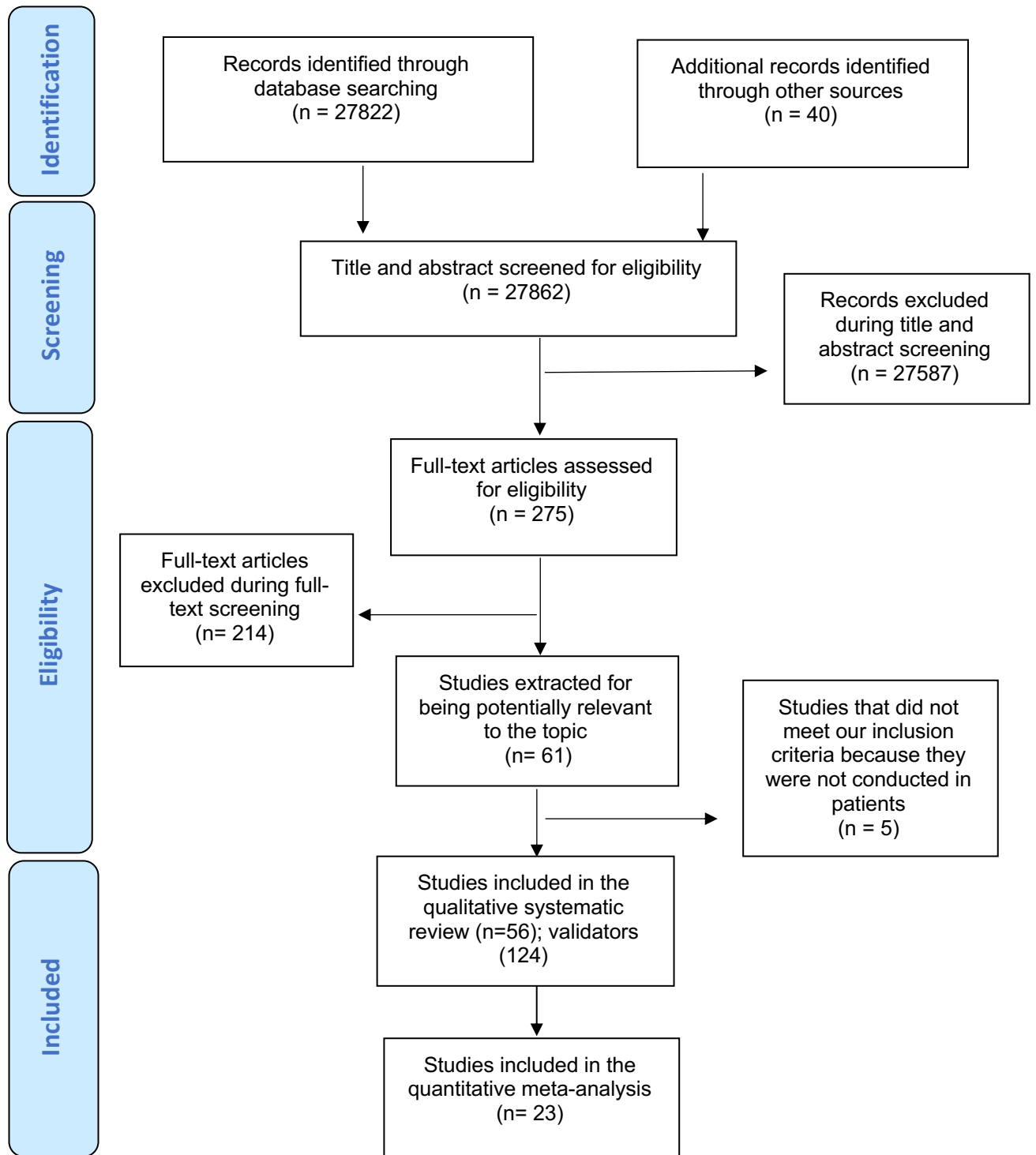


Figure 2. Cumulative risk of psychosis onset in DSM-5-APS/APSS

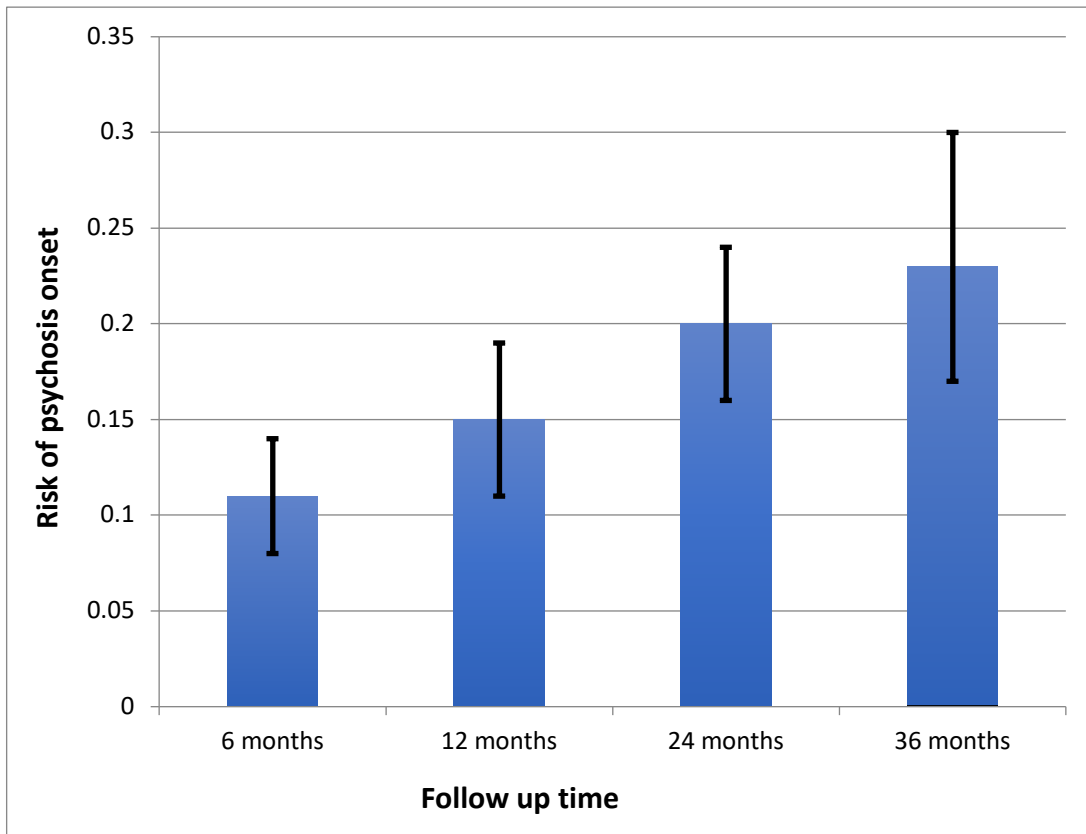


Table 2 to Figure 2. Cumulative risk of psychosis onset in individuals with DSM 5-APS/APSS

Follow-up	n of studies*	Total DSM-5-APS/APSS sample	Cumulative risk of psychosis	95%CI	Q	df	I²	P
6-month	12	824	0.11	0.08-0.14	20.77	11	47.04	0.04
12-month	19	1292	0.15 ^(a)	0.11-0.19	61.02	18	72.14	<0.01
24-month	18	2212	0.2 ^(b)	0.16-0.24	87.22	17	79.36	<0.01
36-month	7	721	0.23	0.17-0.30	22.2	6	72.97	<0.01

* all studies but one¹⁴ refer to APSS; a) 0.104, 95%CI 0.062-0.145 after the fill and trim method; b) 0.139, 95%CI 0.097-0.182 after the fill and trim method.

Table 3. Evidence-based reporting recommendations for future DSM-5-APS clinical research

1	Test the specific DSM-5-APS criteria A to F upfront in a standard psychiatric clinical assessment
2	Report the exact number of patients meeting the specific DSM-5-APS criteria A to F
3	If CHR-P instruments are being used indicate their type and version and stratify the findings across APSS/APS, GRD and BLIPS/BIPS subgroups
4	Preferably use the SIPSv.5.6 for the psychometric assessment of DSM-5-APS; ensure an appropriate training
5	If both clinical DSM-5-APS and psychometric APSS/APS criteria are tested in the same patients, detail their concordance/discordance.

REFERENCES

1. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. Washington DC, 2013.
2. Fusar-Poli P. The Clinical High-Risk State for Psychosis (CHR-P), Version II. *Schizophrenia Bulletin*. 2017;43(1):44-47.
3. Fusar-Poli P, McGorry PD, Kane JM. Improving outcomes of first-episode psychosis: an overview. *World Psychiatry*. 2017;16(3):251-265.
4. McGlashan T WB, Woods S. *The psychosis-risk syndrome: handbook for diagnosis and follow-up*.: Oxford: Oxford University 2010.
5. Miller T, McGlashan T, Rosen J, et al. Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. *Schizophr Bull*. 2003;29:703-715.
6. Miller T, McGlashan T, Woods S, et al. Symptom assessment in schizophrenic prodromal states. *Psychiatr Q*. 1999;Winter; 70:273-287.
7. Yung AR, Yuen HP, McGorry PD, et al. Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. *The Australian and New Zealand journal of psychiatry*. 2005;39(11-12):964-971.
8. Tarbox-Berry SI, Perkins DO, Woods SW, Addington J. Premorbid social adjustment and association with attenuated psychotic symptoms in clinical high-risk and help-seeking youth. *Psychological Medicine*. 2018;48(6):983-997.
9. Braham A, Bannour A, Ben Romdhane A, et al. Validation of the Arabic version of the Comprehensive Assessment of At Risk Mental States (CAARMS) in Tunisian adolescents and young adults. 2014;8(2):147-154.
10. Regier DA, Narrow WE, Clarke DE, et al. DSM-5 field trials in the United States and Canada, Part II: test-retest reliability of selected categorical diagnoses. *The American journal of psychiatry*. 2013;170(1):59-70.
11. Fusar-Poli P, Solmi M, Brondino N, et al. Transdiagnostic psychiatry: a systematic review. *World Psychiatry*. 2019;18(2):192-207.
12. Fusar-Poli P, Cappucciati M, Bonoldi I, et al. Prognosis of Brief Psychotic Episodes: A Meta-analysis. *JAMA Psychiatry*. 2016;73(3):211-220.
13. Fusar-Poli P, Cappucciati M, De Micheli A, et al. Diagnostic and Prognostic Significance of Brief Limited Intermittent Psychotic Symptoms (BLIPS) in Individuals at Ultra High Risk. *Schizophr Bull*. 2017;43(1):48-56.
14. Fusar-Poli P, De Micheli A, Cappucciati M, et al. Diagnostic and Prognostic Significance of DSM-5 Attenuated Psychosis Syndrome in Services for Individuals at Ultra High Risk for Psychosis. *Schizophrenia Bulletin*. 2018;44(2):264-275.
15. Cakmak S, Karaytug MO, Bal U, Tamam L, Tasdemir A. Retrospective evaluation of risk determinants in prodromal period with a group of schizophrenia patients. *Cukurova Medical Journal*. 2016;41(3):437-446.
16. Brucato G, Masucci MD, Arndt LY, et al. Baseline demographics, clinical features and predictors of conversion among 200 individuals in a longitudinal prospective psychosis-risk cohort. *Psychological Medicine*. 2017;47(11):1923-1935.

17. Gerstenberg M, Hauser M, Al-Jadiri A, et al. Frequency and Correlates of DSM-5 Attenuated Psychosis Syndrome in a Sample of Adolescent Inpatients With Nonpsychotic Psychiatric Disorders. *Journal of Clinical Psychiatry*. 2015;76(11):1449-1458.
18. Zoghbi AW, Bernanke JA, Gleichman J, et al. Schizotypal personality disorder in individuals with the Attenuated Psychosis Syndrome: Frequent co-occurrence without an increased risk for conversion to threshold psychosis. *Journal of psychiatric research*. 2019;114:88-92.
19. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.
20. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *Jama*. 2000;Apr 19(15):2008-2012.
21. Riecher-Rössler A, Aston J, Ventura J, et al. [The Basel Screening Instrument for Psychosis (BSIP): development, structure, reliability and validity]. *Fortschr Neurol Psychiatr*. 2008;76(4):207-216.
22. Fusar-Poli P, Tantardini M, De Simone S, et al. Deconstructing vulnerability for psychosis: Meta-analysis of environmental risk factors for psychosis in subjects at ultra high-risk. *European Psychiatry*. 2017;40:65-75.
23. Fusar-Poli P, Rocchetti M, Sardella A, et al. Disorder, not just state of risk: meta-analysis of functioning and quality of life in people at high risk of psychosis. *British Journal of Psychiatry*. 2015;207(3):198-206.
24. Kendler KS. The nosologic validity of paranoia (simple delusional disorder). A review. *Arch Gen Psychiatry*. 1980;37(6):699-706.
25. Fusar-Poli P, Cappucciati M, Borgwardt S, et al. Heterogeneity of Psychosis Risk Within Individuals at Clinical High Risk A Meta-analytical Stratification. *Jama Psychiatry*. 2016;73(2):113-120.
26. Nyaga V, M A, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data *Arch Public Health*. 2014;72:39.
27. Newcombe R. Two-sided confidence intervals for the single proportion: comparison of seven methods. *Stat Med*. 1998;17:857-872.
28. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188.
29. Sterne J, Egger M, Smith G. Systematic reviews in health care: investigating and dealing with publication and other biases in meta-analysis. *BMJ (Clinical research ed)*. 2001;323:101-105.
30. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clinical research ed)*. 1997;315(7109):629-634.
31. Harbord R, Harris R, Sterne A. Updated tests for small-study effects in meta-analyses. *Stat Med*. 2009;9(2):197-210.
32. Steichen T. *Nonparametric Trim and Fill Analysis of Publication Bias in Meta-analysis* 2001.
33. Lipsey M, Wilson D. Practical Meta-analysis. In. Thousand Oaks, CA: Sage Publications; 2000.
34. Kayser J, Tenke CE, Kroppmann CJ, et al. Olfaction in the psychosis prodrome: electrophysiological and behavioral measures of odor detection. *International*

- journal of psychophysiology : official journal of the International Organization of Psychophysiology*. 2013;90(2):190-206.
35. Zhang TH, Li HJ, Woodberry KA, et al. Prodromal psychosis detection in a counseling center population in China: An epidemiological and clinical study. *Schizophrenia Research*. 2014;152(2-3):391-399.
 36. Schultze-Lutter F, Michel C, Ruhrmann S, Schimmelmann BG. Prevalence and Clinical Significance of DSM-5-Attenuated Psychosis Syndrome in Adolescents and Young Adults in the General Population: The Bern Epidemiological At-Risk (BEAR) Study. *Schizophrenia Bulletin*. 2014;40(6):1499-1508.
 37. Addington J, Liu L, Buchy L, et al. North American Prodrome Longitudinal Study (NAPLS 2): The Prodromal Symptoms. *The Journal of nervous and mental disease*. 2015;203(5):328-335.
 38. Ribolsi M, Lin A, Wardenaar KJ, et al. Clinical presentation of Attenuated Psychosis Syndrome in children and adolescents: Is there an age effect? *Psychiatry Research*. 2017;252:169-174.
 39. Schimmelmann BG, Michel C, Martz-Irngartinger A, Linder C, Schultze-Lutter F. Age matters in the prevalence and clinical significance of ultra-high-risk for psychosis symptoms and criteria in the general population: Findings from the BEAR and BEARS-kid studies. *World Psychiatry*. 2015;14(2):189-197.
 40. Chen F, Wang L, Heeramun-Aubeeluck A, et al. Identification and characterization of college students with Attenuated Psychosis Syndrome in China. *Psychiatry Research*. 2014;216(3):346-350.
 41. Gerstenberg M, Theodoridou A, Traber-Walker N, et al. Adolescents and adults at clinical high-risk for psychosis: age-related differences in attenuated positive symptoms syndrome prevalence and entanglement with basic symptoms. *Psychological Medicine*. 2016;46(5):1069-1078.
 42. Gerstenberg M, Theodoridou A, Traber-Walker N, et al. Frequency and Characteristics of the Attenuated Psychosis Syndrome and delineation to other risk profiles in a sample of help-seeking individuals. *Schizophrenia Research*. 2014;153:S317-S318.
 43. Lu Y, Marshall C, Cadenhead KS, et al. Perceptual abnormalities in clinical high risk youth and the role of trauma, cannabis use and anxiety. *Psychiatry Research*. 2017;258:462-468.
 44. Woods S, Walsh B, McGlashan T. Diagnostic reliability and validity of the proposed DSM-5 attenuated psychosis syndrome. *Early Intervention in Psychiatry*. 2012;6:33-33.
 45. Chen F, Wang L, Wang J, Heeramun-Aubeeluck A, Yuan J, Zhao X. Applicability of the Chinese version of the 16-item Prodromal Questionnaire (CPQ-16) for identifying attenuated psychosis syndrome in a college population. *Early Intervention in Psychiatry*. 2016;10(4):308-315.
 46. Koren D, Scheyer R, Reznik N, et al. Basic self-disturbance, neurocognition and metacognition: A pilot study among help-seeking adolescents with and without attenuated psychosis syndrome. *Early intervention in psychiatry*. 2017:1-9.
 47. Koren D, Scheyer R, Stern Y, et al. Metacognition strengthens the association between neurocognition and attenuated psychosis syndrome: Preliminary evidence from a pilot study among treatment-seeking versus healthy adolescents. *Schizophrenia research*. 2019.

48. Zuschlag ZD, Korte JE, Hamner M. Predictors of Lifetime Suicide Attempts in Individuals With Attenuated Psychosis Syndrome. *Journal of Psychiatric Practice*. 2018;24(3):169-178.
49. Mirzakhani H, Sanchez S, Addington J, et al. Risk of violence in Attenuated Psychosis Symptoms Syndrome and its relationship with symptomology. *Schizophrenia Bulletin*. 2017;43:S106-S107.
50. Zhang T, Cui H, Tang Y, et al. Correlation of social cognition and neurocognition on psychotic outcome: a naturalistic follow-up study of subjects with attenuated psychosis syndrome. *Scientific Reports*. 2016;6.
51. Keefe RS, Perkins DO, Gu H, Zipursky RB, Christensen BK, Lieberman JA. A longitudinal study of neurocognitive function in individuals at-risk for psychosis. *Schizophr Res*. 2006;88(1-3):26-35.
52. Long XY, Liu F, Huang N, et al. Brain regional homogeneity and function connectivity in attenuated psychosis syndrome based on a resting state fMRI study. *Bmc Psychiatry*. 2018;18.
53. Perez VB, Woods SW, Roach BJ, et al. Automatic auditory processing deficits in schizophrenia and clinical high-risk patients: forecasting psychosis risk with mismatch negativity. *Biol Psychiatry*. 2014;75(6):459-469.
54. Marshall C, Denny E, Cadenhead KS, et al. The content of attenuated psychotic symptoms in those at clinical high risk for psychosis. *Psychiatry Research*. 2014;219(3):506-512.
55. Marshall C, Deighton S, Cadenhead KS, et al. The Violent Content in Attenuated Psychotic Symptoms. *Psychiatry Research*. 2016;242:61-66.
56. Morita K, Kobayashi H, Takeshi K, Tsujino N, Nemoto T, Mizuno M. Poor outcome associated with symptomatic deterioration among help-seeking individuals at risk for psychosis: a naturalistic follow-up study. *Early Intervention in Psychiatry* 2014;8:24-31.
57. Metzler S, Dvorsky D, Wyss C, et al. Changes in neurocognitive functioning during transition to manifest disease: comparison of individuals at risk for schizophrenic and bipolar affective psychoses. *Psychological medicine*. 2015:1-12.
58. Cornblatt BA, Carrion RE, Auther A, et al. Psychosis Prevention: A Modified Clinical High Risk Perspective From the Recognition and Prevention (RAP) Program. *American Journal of Psychiatry*. 2015;172(10):986-994.
59. Addington J, Liu L, Perkins DO, Carrion RE, Keefe RSE, Woods SW. The Role of Cognition and Social Functioning as Predictors in the Transition to Psychosis for Youth With Attenuated Psychotic Symptoms. *Schizophrenia Bulletin*. 2017;43(1):57-63.
60. Lehembre-Shiah E, Leong W, Brucato G, et al. Distinct Relationships Between Visual and Auditory Perceptual Abnormalities and Conversion to Psychosis in a Clinical High-Risk Population. *JAMA Psychiatry*. 2017;74(1):104-106.
61. Crump FM, Arndt L, Grivel M, et al. Attenuated first-rank symptoms and conversion to psychosis in a clinical high-risk cohort. *Early Intervention in Psychiatry*. 2018;12(6):1213-1216.
62. Masucci MD, Lister A, Corcoran CM, Brucato G, Girgis RR. Motor Dysfunction as a Risk Factor for Conversion to Psychosis Independent of Medication Use in a

- Psychosis-Risk Cohort. *Journal of Nervous and Mental Disease*. 2018;206(5):356-361.
63. Woods S, Addington J, Bearden C, et al. Antidepressant Medication Use in Attenuated Psychosis Syndrome: Community Selection and Outcome. *Early Intervention in Psychiatry*. 2018;12:10-10.
 64. Bedi G, Carrillo F, Cecchi G, et al. Automated analysis of free speech predicts psychosis onset in high-risk youths. *npj Schizophrenia*. 2015;1:15030.
 65. Marshall C, Lu Y, Lyngberg K, et al. Changes in symptom content from a clinical high-risk state to conversion to psychosis. *Early Intervention in Psychiatry*. 2019;13(2):257-263.
 66. Piskulic D, Addington J, Cadenhead KS, et al. Negative symptoms in individuals at clinical high risk of psychosis. *Psychiatry Res*. 2012;196(2-3):220-224.
 67. Corcoran CM, Keilp JG, Kayser J, et al. Emotion recognition deficits as predictors of transition in individuals at clinical high risk for schizophrenia: a neurodevelopmental perspective. *Psychological Medicine*. 2015;45(14):2959-2973.
 68. Addington J, Epstein I, Liu L, French P, Boydell KM, Zipursky RB. A randomized controlled trial of cognitive behavioral therapy for individuals at clinical high risk of psychosis. *Schizophrenia Research*. 2011;125(1):54-61.
 69. Fusar-Poli P, Rutigliano G, Stahl D, et al. Deconstructing Pretest Risk Enrichment to Optimize Prediction of Psychosis in Individuals at Clinical High Risk. *JAMA Psychiatry*. 2016;73(12):1260-1267.
 70. Fusar-Poli P, Schultze-Lutter F, Cappucciati M, et al. The Dark Side of the Moon: Meta-analytical Impact of Recruitment Strategies on Risk Enrichment in the Clinical High Risk State for Psychosis. *Schizophrenia Bulletin*. 2016;42(3):732-743.
 71. Fusar-Poli P, Schultze-Lutter F, Addington J. Intensive community outreach for those at ultra high risk of psychosis: dilution, not solution. *Lancet Psychiatry*. 2016;3(1):18.
 72. Fusar-Poli P, Palombini E, Davies C, et al. Why transition risk to psychosis is not declining at the OASIS ultra high risk service: The hidden role of stable pretest risk enrichment. *Schizophr Res*. 2018;192:385-390.
 73. Fusar-Poli P. Why ultra high risk criteria for psychosis prediction do not work well outside clinical samples and what to do about it. *World Psychiatry*. 2017;16(2):212-213.
 74. Oliver D, Reilly T, Baccaredda Boy O, et al. What Causes the Onset of Psychosis in Individuals at Clinical High Risk? A Meta-analysis of Risk and Protective Factors. *Schizophrenia Bulletin*. 2019.
 75. Radua J, Ramella-Cravaro V, Ioannidis JPA, et al. What causes psychosis? An umbrella review of risk and protective factors. *World Psychiatry*. 2018;17(1):49-66.
 76. Shah JL, Crawford A, Mustafa SS, Iyer SN, Joober R, Malla AK. Is the Clinical High-Risk State a Valid Concept? Retrospective Examination in a First-Episode Psychosis Sample. *Psychiatric Services*. 2017;68(10):1046-1052.
 77. Schultze-Lutter F, Rahman J, Ruhrmann S, et al. Duration of unspecific prodromal and clinical high risk states, and early help-seeking in first-admission

- psychosis patients. *Soc Psychiatry Psychiatr Epidemiol.* 2015;Dec;50(12):1831-1841.
78. Lee T, Lee J, Kim M, Choe E, Kwon J. Can We Predict Psychosis Outside the Clinical High-Risk State? A Systematic Review of Non-Psychotic Risk Syndromes for Mental Disorders. *Schizophr Bull.* 2018;15;44:276-285.
 79. Mishara A, Fusar-Poli P. The phenomenology and neurobiology of delusion formation during psychosis onset: Jaspers, Truman symptoms, and aberrant salience. *Schizophr Bull.* 2013;Mar; 39(2):278-286.
 80. Fusar-Poli P, Rutigliano G, Stahl D, et al. Development and Validation of a Clinically Based Risk Calculator for the Transdiagnostic Prediction of Psychosis. *JAMA Psychiatry.* 2017;74(5):493-500.
 81. Fusar-Poli P, Carpenter WT, Woods SW, McGlashan TH. Attenuated Psychosis Syndrome: Ready for DSM-5.1? In: Cannon TD, Widiger T, eds. *Annual Review of Clinical Psychology, Vol 10.* Vol 10.2014:155-192.
 82. Fusar-Poli P, Hijazi Z, Stahl D, Steyerberg E. The Science of Prognosis in Psychiatry: A Review. *JAMA Psychiatry.* 2018;1;75:1289-1297.
 83. Davies C, Cipriani A, Ioannidis JPA, et al. Lack of evidence to favor specific preventive interventions in psychosis: a network meta-analysis. *World Psychiatry.* 2018;17(2):196-209.
 84. Yung AR, Nelson B. Young people at ultra high risk for psychosis: research from the PACE clinic. *Revista brasileira de psiquiatria (Sao Paulo, Brazil : 1999).* 2011;33 Suppl 2:s143-160.
 85. Lindgren M, Manninen M, Kalska H, et al. Predicting psychosis in a general adolescent psychiatric sample. *Schizophr Res.* 2014;158(1-3):1-6.
 86. Lemos-Giráldez S, Vallina-Fernández O, Fernández-Iglesias P, et al. Symptomatic and functional outcome in youth at ultra-high risk for psychosis: a longitudinal study. *Schizophr Res.* 2009;115(2-3):121-129.
 87. Woods SW, Addington J, Cadenhead KS, et al. Validity of the prodromal risk syndrome for first psychosis: findings from the North American Prodrome Longitudinal Study. *Schizophr Bull.* 2009;35(5):894-908.
 88. Woodberry KA, Seidman LJ, Giuliano AJ, Verdi MB, Cook WL, McFarlane WR. Neuropsychological profiles in individuals at clinical high risk for psychosis: relationship to psychosis and intelligence. *Schizophr Res.* 2010;123(2-3):188-198.
 89. Liu CC, Lai MC, Liu CM, et al. Follow-up of subjects with suspected pre-psychotic state in Taiwan. *Schizophr Res.* 2011;126(1-3):65-70.
 90. Ziermans TB, Schothorst PF, Sprong M, van Engeland H. Transition and remission in adolescents at ultra-high risk for psychosis. *Schizophr Res.* 2011;126(1-3):58-64.
 91. Simon AE, Grädel M, Cattapan-Ludewig K, et al. Cognitive functioning in at-risk mental states for psychosis and 2-year clinical outcome. *Schizophr Res.* 2012;142(1-3):108-115.
 92. Koike S, Takano Y, Iwashiro N, et al. A multimodal approach to investigate biomarkers for psychosis in a clinical setting: the integrative neuroimaging studies in schizophrenia targeting for early intervention and prevention (IN-STEP) project. *Schizophr Res.* 2013;143(1):116-124.

93. DeVylder JE, Muchomba FM, Gill KE, et al. Symptom trajectories and psychosis onset in a clinical high-risk cohort: the relevance of subthreshold thought disorder. *Schizophr Res.* 2014;159(2-3):278-283.
94. Schultze-Lutter F, Klosterkötter J, Ruhrmann S. Improving the clinical prediction of psychosis by combining ultra-high risk criteria and cognitive basic symptoms. *Schizophrenia research.* 2014;154(1-3):100-106.
95. Bang M, Kim KR, Song YY, Baek S, Lee E, An SK. Neurocognitive impairments in individuals at ultra-high risk for psychosis: Who will really convert? *The Australian and New Zealand journal of psychiatry.* 2015;49(5):462-470.
96. Katagiri N, Pantelis C, Nemoto T, et al. A longitudinal study investigating sub-threshold symptoms and white matter changes in individuals with an 'at risk mental state' (ARMS). *Schizophr Res.* 2015;162(1-3):7-13.
97. Chen FZ, Wang Y, Sun XR, et al. Emotional Experiences Predict the Conversion of Individuals with Attenuated Psychosis Syndrome to Psychosis: A 6-Month Follow up Study. *Frontiers in Psychology.* 2016;7.
98. Jacobs E, Kline E, Schiffman J. Practitioner perceptions of attenuated psychosis syndrome. *Schizophrenia Research.* 2011;131(1-3):24-30.
99. Jacobs E, Kline E, Schiffman J. Defining Treatment as Usual for Attenuated Psychosis Syndrome: A Survey of Community Practitioners. *Psychiatric Services.* 2012;63(12):1252-1256.
100. Lee EH-M, Hui CL-M, Ching EY-N, et al. Public Stigma in China Associated With Schizophrenia, Depression, Attenuated Psychosis Syndrome, and Psychosis-Like Experiences. *Psychiatric Services.* 2016;67(7):766-770.
101. Parrish EM, Kim NS, Woodberry KA, Friedman-Yakoobian M. Clinical high risk for psychosis: The effects of labelling on public stigma in a undergraduate population. *Early intervention in psychiatry.* 2018:1-8.
102. Trask CL, Kameoka VA, Schiffman J, Cicero DC. Perceptions of attenuated psychosis in a diverse sample of undergraduates. *Early intervention in psychiatry.* 2018:1-6.