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Development of the PSYCHS: Positive SYmptoms and Diagnostic Criteria for the CAARMS Harmonized with the SIPS

Scott W. Woods[1,2] | Sophie Parker[3,4] | Melissa J. Kerr[5,6] | Barbara C. Walsh[1,2] | S. Andrea Wijtenburg[7] | Nicholas Prunier[8] | Angela R. Nunez[1,2] | Kate Buccilli[5,6] | Catalina Mourgues-Codern[1,2] | Kali Brummitt[9] | Kyle S. Kinney[10] | Carli Trankler[11] | Julia Szacilo[12] | Beau-Luke Colton[3] | Munaza Ali[1,2] | Anastasia Haidar[8] | Tashrif Billah[8] | Kevin Huynh[5,6] | Uzair Ahmed[5,6] | Laura L. Adery[13] | Patricia J. Marcy[14] | Kelly Allott[5,6] | Paul Amminger[5,6] | Celso Arango[15] | Matthew R. Broome[16,17] | Kristin S. Cadenhead[18] | Eric Y. H. Chen[19] | Jimmy Choi[20] | Philippe Conus[21] | Barbara A. Cornblatt[14,22] | Louise Birkedal Glenthøj[23] | Leslie E. Horton[24] | Joseph Kambeitz[25] | Tina Kapur[26] | Matcheri S. Keshavan[27] | Nikolaos Koutsouleris[28,29,30] | Kerstin Langbein[31] | Suzie Lavoie[5,6] | Covadonga Martinez Diaz-Caneja[15] | Daniel H. Mathalon[32,33] | Vijay A. Mittal[34] | Merete Nordentoft[35,36] | Ofer Pasternak[26,37] | Godfrey D. Pearlson[1,20] | Pablo A. Gaspar[38] | Jai L. Shah[39,40] | Stefan Smesny[31] | William S. Stone[27] | Gregory P. Strauss[41] | Jijun Wang[42] | Cheryl M. Corcoran[43] | Diana O. Perkins[44] | Jason Schiffman[45] | Jesus Perez[12,46] | Daniel Mamah[11] | Lauren M. Ellman[10] | Albert R. Powers III[1,2] | Michael J. Coleman[8] | Alan Anticevic[1,2] | Paolo Fusar-Poli[47,48] | John M. Kane[14,22] | Rene S. Kahn[43] | Patrick D. McGorry[5,6] | Carrie E. Bearden[13] | Martha E. Shenton[8,37,49] | Barnaby Nelson[5,6] | Monica E. Calkins[50] | Larry Hendricks[5,6] | Sylvain Bouix[8,51] | Jean Addington[9] | Thomas H. McGlashan[1,2] | Alison R. Yung[3,4,5,52] | The Accelerating Medicines Partnership Schizophrenia

Correspondence
Scott W. Woods, Department of Psychiatry, Yale University School of Medicine, 34 Park Street, New Haven, CT 06519 USA.
Email: scott.woods@yale.edu

Abstract

Aim: To harmonize two ascertainment and severity rating instruments commonly used for the clinical high risk syndrome for psychosis (CHR-P): the Structured

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Accelerating Medicines Partnership Schizophrenia (AMP SCZ) authors are listed in the section Appendix A.

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Interview for Psychosis-risk Syndromes (SIPS) and the Comprehensive Assessment of At-Risk Mental States (CAARMS).

Methods: The initial workshop is described in the companion report from Addington et al. After the workshop, lead experts for each instrument continued harmonizing attenuated positive symptoms and criteria for psychosis and CHR-P through an intensive series of joint videoconferences.

Results: Full harmonization was achieved for attenuated positive symptom ratings and psychosis criteria, and modest harmonization for CHR-P criteria. The semi-structured interview, named Positive SYmptoms and Diagnostic Criteria for the CAARMS Harmonized with the SIPS (PSYCHS), generates CHR-P criteria and severity scores for both CAARMS and SIPS.

Conclusions: Using the PSYCHS for CHR-P ascertainment, conversion determination, and attenuated positive symptom severity rating will help in comparing findings across studies and in meta-analyses.

KEYWORDS
ascertainment, clinical high risk, early detection, psychometrics, severity rating

1 | INTRODUCTION

The clinical high-risk syndrome for psychosis (CHR-P), also known as the At-Risk Mental State (ARMS) or ultra-high risk (UHR) state, was first conceptualized 25 years ago (Yung et al., 1996) and has provided an influential paradigm for early detection and intervention in psychosis. CHR-P syndrome patients are youth and young adults who are symptomatic and impaired and also at risk for developing frankly psychotic disorders (Woods et al., 2001; Woods et al., 2021). A related condition is listed in DSM-5 as Attenuated Psychosis Syndrome (American Psychiatric Association, 2022), one of four specified "Other Specified Schizophrenia Spectrum and Other Psychotic Disorders" (ICD-10 F28) and under the construct of "Conditions for Further Study"; further study has suggested substantial validity (Mensi et al., 2021; Salazar de Pablo et al., 2020). CHR-P syndromes are associated with a meta-analytic 20% probability of developing psychosis at two years, which increases over the long term peaking to 35% at 10-years (de Pablo, Radua, et al., 2021). Most CHR-P individuals who will not develop psychosis will continue displaying other poor mental health outcomes at follow-up (Addington et al., 2019; de Pablo, Besana, et al., 2021). Multiple biological markers predict onset of psychosis in CHR-P patients (Fusar-Poli et al., 2020), including recent evidence that thinning of cerebral cortex precedes and predicts psychosis (Collins et al., 2023). CHR-P is a common, if under-recognized, condition, as evidenced by meta-analytic estimates of point prevalence in the general youth population (1.7%) and in the population of youth presenting for psychiatric care (19.2%) (Salazar de Pablo et al., 2021). A recent bibliographic analysis identified 1637 unique research data publications, with two or more publications originating from 1573 separate institutions in 49 countries (Lee et al., 2022). More than 100 specialty clinics for CHR-P have been organized in multiple countries across six continents (Kotlicka-Antczak et al., 2020).

Two semi-structured interviews have commonly been used to ascertain patients for CHR-P and to rate their severity of illness over time (Andreou et al., 2019; Daneault et al., 2013; Olsen & Rosenbaum, 2006): the Structured Interview for Psychosis-risk Syndromes (SIPS) and the Comprehensive Assessment of At-Risk Mental States (CAARMS) (Miller et al., 1999; Yung et al., 2005). Psychometric properties for both instruments have been extensively studied, and predictive validity of these instruments has been excellent for the conversion to psychosis outcome (AUC = 0.85) (Oliver et al., 2022). Interrater reliability (IRR) for CHR-P ascertainment has also been excellent, both for the SIPS (median kappa across 16 published samples 0.89) (Woods et al., 2019) and the CAARMS (median across three studies 0.845) (Fusar-Poli et al., 2012; Miyakoshi et al., 2009; Paterlini et al., 2019). IRR for attenuated positive symptoms has also been excellent for both SIPS (median ICC across 21 published samples 0.88) (Woods et al., 2019) and CAARMS (median ICC or Pearson *r* across eight studies 0.89) (Braham et al., 2014; Fusar-Poli et al., 2012; Lho et al., 2021; Miyakoshi et al., 2009; Paterlini et al., 2019; Wang et al., 2022; Yokusoglu et al., 2021; Yung et al., 2005).

Recently the US National Institute of Mental Health (NIMH) has spearheaded an effort to harmonize these two instruments (Addington et al., 2023). Harmonization was needed despite identical attenuated positive symptom content and general overall similarity (Schultze-Lutter et al., 2013) because of six important differences in: (1) organization of attenuated positive symptom content into items (Table 1), (2) scaling of items, (3) conceptualization of severity, (4) quantifying symptom frequency, (5) frank psychosis diagnosis criteria (Table 2), and (6) CHR-P syndrome criteria (Tables 3, 4, and 5).

TABLE 1 Content comparison across SIPS, CAARMS, and PSYCHS items.

PSYCHS item	SIPS item	CAARMS item
P1 Unusual Thoughts and Experiences	P1 Unusual Thought Content	P1 Unusual Thought Content
P2 Suspiciousness/ Paranoia	P2 Suspiciousness	P2 Non-Bizarre Ideas
P3 Unusual Somatic Ideas	P1 Unusual Thought Content	P2 Non-Bizarre Ideas
P4 Ideas of Guilt	P1 Unusual Thought Content	P2 Non-Bizarre Ideas
P5 Jealous Ideas	P1 Unusual Thought Content	P2 Non-Bizarre Ideas
P6 Unusual Religious Ideas	P1 Unusual Thought Content	P2 Non-Bizarre Ideas
P7 Erotomanic Ideas	P3 Grandiose Ideas	P2 Non-Bizarre Ideas
P8 Grandiosity	P3 Grandiose Ideas	P2 Non-Bizarre Ideas
P9 Auditory Perceptual Abnormalities	P4 Perceptual Abnormalities	P3 Perceptual Abnormalities
P10 Visual Perceptual Abnormalities	P4 Perceptual Abnormalities	P3 Perceptual Abnormalities
P11 Olfactory Perceptual Abnormalities	P4 Perceptual Abnormalities	P3 Perceptual Abnormalities
P12 Gustatory Perceptual Abnormalities	P4 Perceptual Abnormalities	P3 Perceptual Abnormalities
P13 Tactile Perceptual Abnormalities	P4 Perceptual Abnormalities	P3 Perceptual Abnormalities
P14 Somatic Perceptual Abnormalities	P4 Perceptual Abnormalities	P3 Perceptual Abnormalities
P15 Disorganized Communication	P5 Disorganized Communication	P4 Disorganized Speech

Note: Green text indicates the same health experience content is contained in the same item in SIPS 5.6.1 and CAARMS 2015; red text indicates the same health experience content is contained in different items in SIPS 5.6.1 and CAARMS 2015.

These six differences make it challenging if not impossible to translate severity scores or diagnoses from one instrument to another and consequently generate uncertainty about comparing findings from studies that use one but not the other (Addington et al., 2023). In fact, some authors have described the state of assessment in the CHR-P field as one of "near-Babylonian" confusion (Schultze-Lutter et al., 2011). Using both instruments in a single study has generally been impractical due to participant burden and cost considerations. Therefore, harmonization seemed to be the only solution.

The goal of this effort was to create a new instrument that harmonizes the CAARMS and the SIPS to the degree feasible based on current knowledge. The harmonized instrument is called Positive SYmptoms and Diagnostic Criteria for the CAARMS Harmonized with the SIPS (PSYCHS). It generates fully harmonized positive symptom ratings, provides for scoring of all CAARMS and SIPS positive symptom items from a single interview, fully harmonizes psychosis criteria, and generates partially harmonized CHR/UHR diagnostic criteria for both the CAARMS and the SIPS. This paper describes the methods and results for the harmonization in detail, including limits to harmonization; it also briefly outlines our implementation in the ongoing Accelerating Medicines Partnership® Schizophrenia (AMP® SCZ) observational study (Brady et al., 2023).

2 | METHODS

2.1 | Harmonization process

The initial harmonization process began when the NIMH hosted a workshop on February 13th and 14th 2020, attended by 38 international participants and described in the companion report (Addington et al., 2023). After the workshop, the lead experts for the SIPS and CAARMS (SWW and ARY) began a series of videoconference meetings in April 2020 facilitated by a NIMH program officer (SAW). These meetings considered workshop recommendations and unresolved issues and were generally held weekly for 2 h. Beginning in January 2021, additional members with extensive practical experience with the CAARMS (SP, MJK) and the SIPS (BCW) joined these meetings.

Meeting time was spent reviewing the literature, comparing item content between SIPS version 5.6.1 (Keefe et al., 2021; Walsh, 2021) and CAARMS 2015 (Yung et al., 2015), ensuring that all attenuated positive symptom content in both instruments was captured in the PSYCHS by verbatim interviewer inquiries, reformulating the joint item content into new and distinct items (Table 1 Content comparison across SIPS, CAARMS, and PSYCHS items), ensuring the consistency of measurement concepts across items, harmonizing scaling, ensuring that the harmonized scale anchors for each item were distinct, ordered, and graded according to similar intervals within each measurement concept, and crafting interviewer and scoring instructions. All decisions were made by consensus, and minutes were taken by SAW.

2.2 | Limits to harmonization

The initial charge in the NIMH-hosted workshop was to fully harmonize the two instruments. The workshop ended with incomplete progress, however, due to the number and difficulty of the challenges presented. After more than a year of intensive weekly meetings, the working group members agreed that it was possible to fully harmonize the assessment of attenuated positive symptoms. It was also possible to fully harmonize the diagnostic criteria for frank psychosis used for excluding CHR-P at ascertainment and for determining conversion/transition to frank psychosis. Although some progress was made in harmonizing CHR-P syndrome criteria, in the end, the different conceptualizations of the CHR-P syndrome proved too difficult to reconcile, and the group focused on designing the PSYCHS to generate data for both CAARMS and SIPS CHR-P syndrome criteria.

TABLE 2 Frank psychosis criteria for the SIPS and the CAARMS and the harmonized PSYCHS criteria.

Psychosis criteria domain	Instrument		
	SIPS 5.6.1	CAARMS 2015	PSYCHS
Severity	Any of SIPS P1–P5 = 6	Any of CAARMS P1–P4 = 6, or P3 = 5	Any of PSYCHS P1–P15 = 6
Timeframe	Lifetime	Lifetime	Lifetime
Frequency	1 h per day or more at an average frequency of 4 days a week	3 or more days a week – 1 h or more a day, or at least daily	3 or more days a week – 1 h or more a day, or at least daily
Duration	1 month	1 week or longer unless new or increased antipsychotic	1 week or longer unless new or increased antipsychotic
Danger	Frequency and duration waived if seriously disorganizing or dangerous	None	Frequency and duration waived if imminently dangerous[a]

Note: Red text indicates differences between SIPS and CAARMS, green text indicated harmonized criteria for psychosis.
[a]Physically or to personal dignity or to social/family networks.

TABLE 3 PSYCHS CHR-P criteria based on attenuated positive symptoms.

	SIPS CHR-P Criteria from PSYCHS	CAARMS UHR Criteria from PSYCHS
Domain	**Current APSS Progression**	**Subthreshold Positive Symptom Intensity**
Severity	Any positive symptom scored 3–5	Any positive symptom scored 3–5
Timeframe	Past month	Past 12 months
Attribution	At least one symptom scored 3–5 is *not* explained better by another DSM disorder	At least one symptom scored 3–5 occurred outside of peak intoxication from a substance known to be associated with psychotic experiences (e.g., hallucinogens, amphetamines, cocaine)
Frequency	At least one symptom also occurred on average ≥ once/week	At least one symptom also occurred one or more days a month – more than 1 h a day or 3 or more days a week
Worsening	At least one symptom also began or worsened in the past year	None
Functional Change	None	
or Functional Deficit	None	
Criteria	None	**Subthreshold Positive Symptom Frequency**
Severity	None	Any positive symptom scored 6
Timeframe	None	Past 12 months
Frequency	None	At least one symptom occurred 1 day a month but less than 2 days – more than 1 h a day or 3 or more but less than 7 days a week
Functional Change	None	
or Functional Deficit	None	
Current Statuses	Also provides criteria for Lifetime, Persistence and Partial and Full Remission	None

Note: Green text indicates revised from original instrument with strike-through indicating its removal, red text indicates differences between SIPS and CAARMS remaining in the PSYCHS.
Abbreviations: APSS, attenuated positive symptom syndrome.

PSYCHS developers intended to keep the average administration time for the initial assessment version to no more than 90 min on average and no more than 60 min on average for the follow-up version, both broadly consistent with CAARMS and SIPS administration times. To meet these participant- and interviewer-burden goals, it was necessary to focus exclusively on diagnostic assessment and on attenuated positive symptoms that are required for that assessment. As a result, assessments for negative, disorganized, and general symptoms in the SIPS and for cognitive change, negative symptoms, behavioural change, motor/physical changes, and general psychopathology in the CAARMS were not included (see section 4.2 Limitations).

2.3 | Implementation process

Harmonization was completed by December 2021. Work then shifted to implementing the instrument in Research Electronic Data Capture (REDCap) and the in-house Research Project Management System

TABLE 4 PSYCHS CHR-P criteria based on brief fully psychotic symptoms.

	SIPS CHR-P Criteria from PSYCHS	CAARMS UHR Criteria from PSYCHS
Domain	**Current BIPS Progression**	**Brief Limited Intermittent Psychotic Symptoms (BLIPS)**
Severity	Any positive symptom scored 6	Any positive symptom scored 6
Timeframe	Past month	Past 12 months
Attribution	At least one symptom scored 6 is *not* explained better by another DSM disorder	At least one symptom scored 6 occurred outside of peak intoxication from a substance known to be associated with psychotic experiences (e.g., hallucinogens, amphetamines, cocaine)
Frequency	At least one symptom also occurred ≥ several minutes a day at least once in the past month	At least one symptom also occurred three or more days a week – more than 1 h a day or at least daily
Duration	None	Less than 1 week
Worsening	At least one symptom also began or worsened in the past 3 months	None
Functional Change	None	
or Functional Deficit	None	
Current Statuses	Also has criteria for Lifetime, Persistence and Partial and Full Remission	None

Note: Green text indicates revised from original instrument with strike-through indicating its removal, red text indicates differences between SIPS and CAARMS remaining in the PSYCHS.
Abbreviations: BIPS, brief intermittent psychosis syndrome; BLIPS, brief limited intermittent psychotic symptoms.

TABLE 5 PSYCHS CHR-P criteria based on trait vulnerability and functional impairment.

	SIPS CHR-P Criteria from PSYCHS	CAARMS UHR Criteria from PSYCHS
Domain	**Current GRD Progression**	**Vulnerability group**
Family Hx	Psychosis in first degree relative	Psychosis in first degree relative
or Schizotypy	or Current or past SPD in participant	or Current or past SPD in participant
Timeframe	Past month	Past year
Functional Change	≥ 30% drop in the SOFAS, over the past month, relative to 12 months prior	≥ 30% drop in the SOFAS, sustained ≥1 month, within the past year, relative to premorbid level
or Functional Deficit	None	or SOFAS of 50 or less for past 12 months or longer
Current Statuses	Also contains criteria for Lifetime, Persistence and Partial and Full Remission	None

Note: Green text indicates revised from original instrument, red text indicates differences between SIPS and CAARMS remaining in the PSYCHS.
Abbreviations: GRD, genetic risk and deterioration; SOFAS, social and occupational functioning assessment scale.

(RPMS), in collaboration with three projects included in the AMP SCZ consortium: the Psychosis-risk Outcomes Network (ProNET; SWW, CEB, and JMK, PIs), the Trajectories and Predictors in the CHR-P for Psychosis Population: Prediction Scientific Global Consortium (PRESCIENT; BN and PJM, PIs), and the Psychosis Risk Evaluation, Data Integration and Computational Technologies (PREDICT) Data Processing, Analysis and Coordination Center (DPACC; MES and RSK, PIs).

Implementation of the initial assessment version in REDCap and RPMS was completed by May 2022. Rater training and certification then began, for which JA and AN joined the working group meetings, and consensus calls were organized. Data collection for the initial assessment version began in the large observational study component of AMP SCZ in June 2022. Implementation of the follow-up version was completed by July 2022.

3 | RESULTS

Results are presented for the fully harmonized acquisition of attenuated positive symptoms, the fully harmonized psychosis determination, and the partially harmonized and parallel SIPS/CAARMS CHR/UHR determinations. Materials available and current use in AMP SCZ are also briefly described.

3.1 | Fully harmonized attenuated positive symptom acquisition

Full harmonization of the CAARMS and the SIPS attenuated positive symptoms was achieved in the areas of: symptom content, content organization into items, measurement concepts within each item, scaling of severity level, anchors for each level for each measurement concept for each item, fully-structured inquiries about patient health experiences mapping onto each item, and scoring of severity.

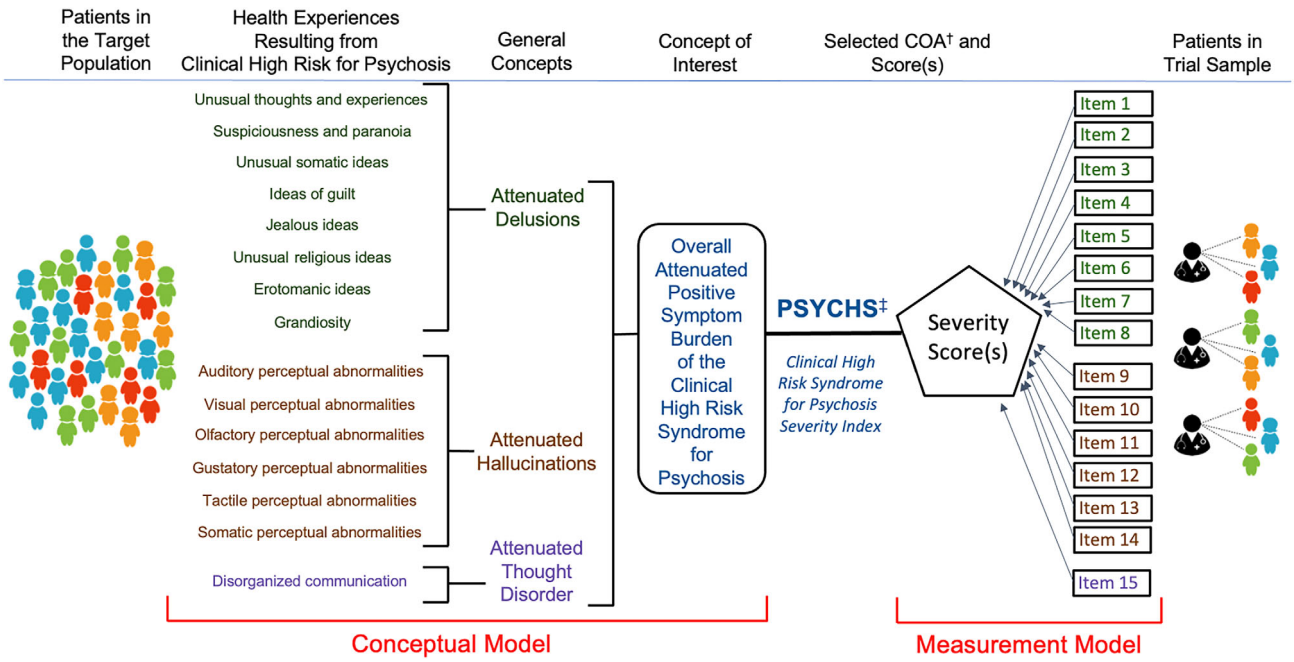

FIGURE 1 COA† conceptual framework for the PSYCHS‡ symptom severity assessment. The conceptual framework consists of a conceptual model (left side of panel) and a measurement model (right side of panel). In the conceptual model, attenuated positive symptom-related health experiences resulting from the Clinical High Risk Syndrome for Psychosis are organized into 15 distinct symptoms. These health experiences are organized into three general concepts: (1) attenuated delusions, (2) attenuated hallucinations, and (3) attenuated thought disorder. Together the three general concepts form the concept of interest. In the measurement model, 15 measurement items corresponding to the health experience areas captured by the PSYCHS yield severity scores that in turn are used to compute a Clinical High Risk Syndrome for Psychosis severity index. † Clinical Outcomes Assessment. ‡ Positive SYmptoms and Diagnostic Criteria for the CAARMS Harmonized with the SIPS.

Figure 1 shows the conceptual framework underlying attenuated positive symptom acquisition in the PSYCHS. Following US Food and Drug Administration guidance (U.S. Department of Health and Human Services et al., 2022), the framework consists of a conceptual model and a measurement model. In the conceptual model, attenuated positive symptom-related health experiences resulting from CHR-P are organized into 15 distinct symptoms. Each of these is captured in the PSYCHS by two or more verbatim Inquiries and semi-structured Follow-up Questions. These health experiences are organized into three general concepts: (1) attenuated delusions, (2) attenuated hallucinations, and (3) attenuated thought disorder. Together the three general concepts form the concept of interest (Overall Attenuated Positive Symptom Burden of the Clinical High Risk Syndrome for Psychosis). In the measurement model, the PSYCHS is a Clinical Outcomes Assessment (COA) instrument as defined by FDA (U.S. Department of Health and Human Services et al., 2022) and yields a CHR-P attenuated positive symptom severity index comprising severity scores from 15 measurement items corresponding to 15 health experience areas captured by the PSYCHS.

3.1.1 | Content coverage

Review of the separate instrument instructions, manuals, and positive symptom inquiries and items revealed identical positive symptom content across the SIPS and CAARMS.

3.1.2 | Content organization into items

Although positive symptom content was identical, the same content was organized across the SIPS and the CAARMS into different items and into a different number of items based on differing formulations of psychopathology. Table 1 (Content comparison across SIPS, CAARMS, and PSYCHS items) shows how attenuated positive symptom content mapped across the instruments. For example, unusual somatic ideas were captured in P1 of the SIPS (Unusual Thought Content) because they were neither paranoid nor grandiose in nature and so did not belong in SIPS P2 or P3; the CAARMS, however, captured unusual somatic ideas in P2 (Non-Bizarre Ideas) because they were not bizarre in the sense that they were theoretically possible. Another example is grandiosity, which was considered an independent item in the SIPS (P3) but designated as a component of Non-Bizarre Ideas (P2) in the CAARMS. No procedure could be devised to harmonize the two instruments by reorganizing content into just a handful of items without losing the integrity of individual items that have been strongly predictive of future psychosis in previous studies (Cannon et al., 2016). Thus, Unusual Somatic Ideas, Ideas of Guilt, Jealous Ideas, and Unusual Religious Ideas each required separate items in the PSYCHS (Table 1 and Figure 1).

Since at least nine items would be needed to capture all of the CAARMS and SIPS attenuated positive symptom content, consideration was given to whether further splitting was desirable. Erotomania

was separated from other forms of grandiosity, consistent with evidence that erotomania can constitute a distinct psychotic syndrome (Segal, 1989). Previously erotomania was rated in the SIPS under P3 grandiosity and in the CAARMS under P2 Non-Bizarre Ideas. We elected to divide the single perceptual abnormalities in both CAARMS and SIPS into six items: auditory, visual, olfactory, gustatory, tactile, and somatic, based on evidence that the combined perceptual abnormalities items predicted future psychosis poorly (Katsura et al., 2014; Perkins et al., 2015; Zhang et al., 2018) and mixed evidence that abnormalities of specific perceptual modalities may predict future psychosis differently (Ciarleglio et al., 2019; Lehembre-Shiah et al., 2017; Niles et al., 2019). Content of Disorganized Communication Expression was already harmonized (PSYCHS P15). Thus, the PSYCHS was formulated with 15 attenuated positive symptom items (Table 1).

One experience, nihilistic ideas, had been captured in the CAARMS under P2 Non-Bizarre Ideas and in the SIPS under P1 Unusual Thought Content. We considered formulating nihilistic ideas into a separate item, perhaps along with perplexity and delusional mood, but in the end felt that additional psychopathology research was needed to properly construct a severity gradient and that for now nihilism should be placed within PSYCHS P1 (Unusual Thoughts and Experiences).

The name for P1 in both SIPS and CAARMS is Unusual Thought Content, and both instruments organize mental events and experiences such as thought insertion into this item. This organization is consistent with psychopathological classification of thought insertion as a delusion rather than a hallucination (American Psychiatric Association, 2013) due to the lack of a sensory component. Following Fish (Hamilton, 1984), who considered mental events such as thought insertion to be *experiences*, the name for PSYCHS P1 was changed to Unusual Thoughts and Experiences.

3.1.3 | Attenuated positive symptom measurement concepts

Positive symptom severity is complex and multidimensional, and symptom severity anchors in both SIPS and CAARMS have always contained mixtures of measurement concepts in the item anchors. Attention to distinguishing measurement concepts within the anchors has become more detailed and explicit with subsequent revisions for each instrument. With the revision from version 5.6 to 5.6.1 in 2017, SIPS anchors have been designed so that each item contains a graded description of each measurement concept for each severity level.

This structure was maintained in the PSYCHS. Each item is conceptualized as composed of, and each scale level for each symptom/experience is closely anchored for, three or four measurement concepts: (1) symptom description (all items); (2) symptom tenacity (for attenuated delusion items P1 to P8), symptom source (for attenuated hallucination items P9 to P14), or symptom self-correction (for attenuated disorganized communication item P15); (3) distress due to the symptom (all items except P8 Grandiosity); and (4) interference (with other thoughts, feelings, social relations and/or behaviour) due to the symptom (all items). Definitions for each measurement concept are included in Table S1 in Appendix S1, and an example of their use in the PSYCHS for P2 Suspiciousness/Paranoia is included in Table S2 in Appendix S1.

The measurement concepts are synthesized into a single rating for the item as follows: the first two measurement concepts are co-primary and generally determine the item's single rating. For example, if an interviewer judges that symptom description matches anchor text for 5, and symptom tenacity/source/self-correction also matches anchor text for 5, the item single rating for that timeframe is 5.

The third and fourth measurement concepts (distress and interference) are secondary. In the example above, the secondary measurement concepts do not contribute to the single rating. The secondary measurement concepts only contribute to the single rating in the situation when the interviewer determines that the co-primary measurement concepts do not agree. For example, when the interviewer judges that symptom description matches anchor text for 4 but symptom tenacity/source/self-correction matches anchor text for 5, or vice-versa, the interviewer should take into account anchor text for distress due to the symptom and for interference due to the symptom. If *either* distress *or* impairment due to the symptom matches anchor text in the 5 or 6 range, the single rating for that item will be 5. If *both* distress *and* impairment due to the symptom match anchor text in the 4 or lower range, the single rating for that item will be 4.

Among the attenuated hallucinations items (P9–P14), the focus of the second measurement concept is on the perceived source of the perception, the degree to which the experience is perceived to arise from a real source as opposed to arising from one's own thoughts. The concept of perceived source is derived from the CAARMS and represents a change for the SIPS. Previously the SIPS P4 Perceptual Abnormalities item considered the degree to which the sensory experience was believed to be real instead of the degree to which it was perceived as real. Colleagues occasionally pointed out the inconsistency in the SIPS in having a perceptual item rely on a delusional interpretation, and so the SIPS developers on the team were amenable to adopt the CAARMS procedure. Independent perceptual and delusional items may facilitate research focusing on the co-occurrence and sequencing of onset of attenuated delusions and hallucinations (Mourgues et al., 2023; Smeets et al., 2015).

Thus, the PSYCHS gives strong and often exclusive priority to the two primary measurement concepts in determining attenuated positive symptom severity/intensity. The rationale for this approach was that distress or disability associated with attenuated positive symptoms may be affected by other factors in addition to actual attenuated positive symptom severity, such as depression or anxiety, consistent with a recent empirical analysis (Wilson et al., 2020).

3.1.4 | Harmonized attenuated positive symptom item scaling

Attenuated positive symptom item scaling differed between the CAARMS and SIPS. For the SIPS, the fully psychotic range was limited to level 6, the subsyndromal or CHR-P range was 3–5, and the non-pathological range was 0–2 for all five attenuated positive symptom items. For the CAARMS, the same was true for items P1 and P2, but for CAARMS P3 (perceptual abnormalities) the fully psychotic range was 5–6, the subsyndromal or CHR-P range was 3–4, and the non-pathological range was 0–2, while for CAARMS P4 (conceptual disorganization), the fully psychotic range was limited to level 6, the subsyndromal or CHR-P range was 4–5, and the non-pathological range was 0–3.

As part of the harmonization process, CAARMS developers felt that consistency across items was an advantage for raters, and anchor content for the PSYCHS was crafted so that the severity gradient reflected frank psychosis at level 6, the subsyndromal or CHR-P range at 3–5, and the non-pathological range at 0–2 for all 15 attenuated positive symptom items. On careful inspection of the original instrument anchors, it was possible to meld content from the two instruments so that, for example, level 6 on the PSYCHS attenuated hallucinations items retained consistency with levels 5 and 6 from CAARMS P3 while also retaining consistency with the distinction between levels 5 and 6 on SIPS P4.

The labels for the anchor levels also differed slightly across the original instruments. For SIPS 5.6.1, levels 0–6 were labelled, respectively: Absent; Questionably Present; Mild; Moderate; Moderately Severe; Severe but not Psychotic; and Severe and Psychotic. For CAARMS 2015, levels 0–6 were labelled, respectively: Never, absent; Questionable; Mild; Moderate; Moderately severe; Severe; and Psychotic & severe. The working group agreed that these could be fully harmonized as: Absent; Questionable; Mild; Moderate; Marked; Severe but not Psychotic; and Psychotic and Very Severe.

3.1.5 | Harmonized attenuated positive symptom item anchors

Once the scaling challenges were surmounted, it was conceptually straightforward to meld text from the original instrument anchors into harmonized text for each measurement concept, for each anchor, and for each item. Careful attention was paid so that within each measurement concept for each item, the seven (0–6) levels described different severity levels of the same content, that the seven levels were each distinct from one another, that each adjacent level was ordered relative to its neighbours, and that a consistent increasing gradient of severity existed across levels within each measurement concept. The anchor sets for each item were further scrutinized for consistency with the anchor labels, such that, for example, the word "marked" was not used in an anchor under Severe but not Psychotic. Lastly, the anchors within each measurement concept were evaluated across items, so that, for example, the same words were not used for differing levels across items.

3.1.6 | Harmonized attenuated positive symptom inquiries

Since the CAARMS and the SIPS covered identical overall positive symptom content, harmonizing verbatim inquiries about participant's health experiences was relatively straightforward. The two sets of inquiries were merged, and redundancies were eliminated.

3.1.7 | Concept of severity

The two instruments conceptualize severity similarly in most regards, as reviewed above, and when there is variability of severity within the measurement interval both instruments capture the highest severity during that interval. There is one important difference, however (Addington et al., 2023). The SIPS conceptualizes the synthesis of the measurement concepts for a particular item over the past month as *severity*. The CAARMS conceptualizes the same measurement concepts over the same recall interval as *intensity* rather than as severity and adds an additional severity measurement concept of symptom *frequency*. Intensity and frequency are then combined to yield CAARMS severity. Since this difference could not be harmonized, the PSYCHS generates ratings for both SIPS and CAARMS conceptualizations of severity. To acknowledge this difference, the synthesis of the four harmonized severity-relevant measurement concepts in the PSYCHS items (not including frequency) is termed *severity/intensity* within the instrument. In addition, a new severity score native to the PSYCHS is calculated as the sum of PSYCHS items P1–P15 (range 0–90).

3.1.8 | SIPS item generation and scoring of SIPS severity

As described above (section 3.1.2 Content organization into items), the SIPS and CAARMS contain identical overall attenuated positive symptom content but organize the same content into items differently. Attenuated positive symptoms that were included in different items in the SIPS and CAARMS were therefore split out into separate items in the PSYCHS (Table 1 Content Comparison across SIPS, CAARMS, and PSYCHS items). This feature allows then for *reassembling* the original SIPS item structure from the PSYCHS data collection and for calculating SIPS severity scores from PSYCHS data when desired.

Severity scores for the original five SIPS items are generated from the PSYCHS as follows. SIPS P1 content was divided in the PSYCHS into five items (PSYCHS P1, P3, P4, P5, and P6, Table 1). When rating the SIPS over the past month timeframe, interviewers

are instructed to rate the highest severity for any of the component symptoms present in an item. Therefore the severity of SIPS P1 may be calculated from the PSYCHS by taking the highest of PSYCHS P1, P3, P4, P5, and P6 severity/intensity. SIPS P2 and PSYCHS P2 content are identical (Table 1), and therefore SIPS P2 severity equals PSYCHS P2 severity/intensity. SIPS P3 content was split in the PSYCHS into two items (PSYCHS P7 and P8, Table 1), and therefore SIPS P3 severity is equal to the higher of PSYCHS items 7 and 8. SIPS P4 content was split in the PSYCHS into six items (PSYCHS P9–P14, Table 1), and therefore SIPS P4 severity is equal to the highest of PSYCHS items P9–P14. SIPS P5 and PSYCHS P15 content are identical (Table 1), and therefore SIPS P5 severity equals PSYCHS item 15.

The SIPS total attenuated positive symptom severity score is the sum of SIPS items P1–P5 (range 0–30) as per usual practice.

3.1.9 | CAARMS item generation and scoring of CAARMS severity

CAARMS interviewers rate intensity and frequency for each item (section 3.1.7 Concept of severity). Consistent with previous practice (Hartmann et al., 2020; Morrison et al., 2012), CAARMS severity is equal to the product of intensity and frequency. The PSYCHS includes CAARMS frequency ratings for each of the 15 PSYCHS items. Similarly as for the original SIPS items (section 3.1.8 above), the severity/intensity and frequency ratings for the 15 PSYCHS items permit *reassembling* the original CAARMS item structure also from the PSYCHS data collection and for calculating CAARMS severity scores from PSYCHS data when desired.

Severity scores for the original four CAARMS items are generated from the PSYCHS as follows. CAARMS P1 and PSYCHS P1 content are identical (Table 1 Content comparison across SIPS, CAARMS, and PSYCHS items), and therefore CAARMS P1 intensity equals the product of PSYCHS P1 severity/intensity and frequency. CAARMS P2 content was divided in the PSYCHS into seven items (PSYCHS P2–P8, Table 1). When rating the CAARMS over the past month timeframe, interviewers are instructed to rate the intensity and frequency for the component symptom whose product is the highest of the component symptoms present in an item. Therefore the severity of CAARMS P2 may be calculated from the PSYCHS by taking the highest of the seven products of severity/intensity and frequency for PSYCHS items P2–P8. CAARMS P3 content was split in the PSYCHS into six items (PSYCHS P9–P14, Table 1), and therefore CAARMS P3 severity may be calculated from the PSYCHS by taking the highest of the six products of severity/intensity and frequency for PSYCHS items P9–P14. CAARMS P4 and PSYCHS P15 content are identical (Table 1), and CAARMS P4 severity may be calculated from the PSYCHS from the product of severity/intensity and frequency for PSYCHS items P15.

The CAARMS total attenuated positive symptom severity score is the sum of the four CAARMS P1–P4 severity scores (range 0–144).

3.2 | Fully harmonized psychosis determination

CAARMS 2015 and SIPS 5.6.1 criteria for frank psychosis, used for excluding fully psychotic participants at study ascertainment and as criteria for conversion/transition to psychosis during study follow-up, differed in four of five domains, being identical only on the rating time frame (Table 2 Frank psychosis criteria for the SIPS and the CAARMS and the harmonized PSYCHS criteria). Since conversion/transition was a frequently used outcome measure, the authors felt that it was essential to harmonize these criteria. Moreover, a study wherein both SIPS and CAARMS criteria were derived from a single modified CAARMS interview found considerable disagreement on presence of frank psychosis (Fusar-Poli, Cappucciati, Rutigliano, et al., 2016). The harmonization of attenuated positive symptom severity (see above) permitted full agreement in the severity domain, and consensus was reached on the remaining three domains, as described in sections 3.2.1 and 3.2.2. The fully-harmonized psychosis criteria are included in Appendix S1.

3.2.1 | Harmonization of duration and frequency criteria for frank psychosis

The SIPS has required a duration of fully psychotic symptoms of 1 month to qualify for psychotic disorder, consistent with DSM-5 criteria for schizophrenia (American Psychiatric Association, 2022). CAARMS duration criteria were greater than or equal to 1 week. In practice, the SIPS duration and frequency criteria could permit a frank psychosis determination in as little as 16 days if the psychotic-level symptoms were experienced daily (which averages to 4 days a week for a month). However, practitioners, patients, and their families were often reluctant to wait that long to institute treatment for frank psychosis and the SIPS developers were agreeable to adopt the CAARMS frequency and duration criteria (Table 2 Frank psychosis criteria for the SIPS and the CAARMS and the harmonized PSYCHS criteria).

3.2.2 | Harmonization of the frank psychosis dangerousness criterion

The SIPS waiver of frequency and duration criteria when fully psychotic symptoms were disorganizing or dangerous had been a sticking point in the initial NIMH workshop (Addington et al., 2023). This waiver was meant in part to mitigate the risk of delayed SIPS diagnosis of psychosis due to the 1 month duration criterion when the need for treatment was immediate. The shorter CAARMS duration requirement, and its exception for cases that received new or increased antipsychotic medication, mitigated the risks associated with the longer SIPS duration criteria to some extent. However, those risks were not mitigated entirely. In addition, the SIPS waiver of the frequency and duration criteria when fully psychotic symptoms were disorganizing or dangerous also functioned to mitigate a difficulty with the duration

criteria when evaluating a person shortly after onset and when frank psychosis was clear-cut. This difficulty is that clinicians and researchers can be left in limbo without a psychosis determination if the participant is unable to be reevaluated a week later. That situation can occur around the time of conversion/transition if frank psychosis leads the participant to disengage from a clinical service or to be unable or unwilling to continue research participation. The SIPS waiver of the frequency and duration criteria resolves this difficulty in cases where symptoms are so clearly indicative of frank psychosis that they are associated with danger to self or others.

During the course of the intensive follow-up meetings, the CAARMS developers found these arguments reasonably compelling and were agreeable to adopt the SIPS waiver, so long as the phrase "seriously disorganizing or dangerous" was reworded. SIPS developers had on occasion been asked questions about what "seriously disorganizing" meant, or needed to correct confusion between "disorganizing" and disorganization symptoms, and thus the authors agreed on substituting "imminently dangerous, physically or to personal dignity or to social/family networks." These criteria enable a psychosis diagnosis to be made at a single visit when, for example, a person's dignity and reputation are threatened by psychotic behaviour or when their or another's life is endangered due to psychotic thinking or behaviour.

3.3 | Modestly harmonized and parallel CHR/UHR determination

Following the CAARMS, the SIPS has always generated three CHR/UHR syndromes based on the same three principles: (1) presence of attenuated positive symptoms (CAARMS Subthreshold Positive Symptom Intensity and Subthrehold Positive Symptom Frequency/SIPS Attenuated Positive Symptoms Syndrome, Table 3 PSYCHS CHR-P criteria based on attenuated positive symptoms), (2) presence of brief fully psychotic symptoms (CAARMS Brief Limited Intermittent Psychotic Symptoms/SIPS Brief Intermittent Psychosis Syndrome, Table 4 PSYCHS CHR-P criteria based on brief fully psychotic symptoms), and (3) presence of trait vulnerability and functional decline (CAARMS Vulnerability group/SIPS Genetic Risk and Functional Deterioration, Table 5 PSYCHS CHR-P criteria based on trait vulnerability and functional impairment). The detailed definitions for each of the three CHR/UHR syndromes differed, however. In the end, the working group was able to reconcile these differences only to a relatively minor degree (sections 3.3.1 and 3.3.2).

For the syndromes based on presence of attenuated positive symptoms (Table 3), the achievement of symptom severity harmonization offered promise, and the frequency criteria could potentially have been harmonized, but neither investigator group could compromise on the several remaining differences. The SIPS required attenuated positive symptoms to have been present in the past month and considered them in remission if they were no longer present in the past month (Woods et al., 2014), while the CAARMS permitted attenuated positive symptoms to have been present at any time in the past year. A compromise period of 6 months was proposed at the workshop (Addington et al., 2023), but during the extended discussions SIPS developers could not agree that symptoms no longer present in the past month should not be considered in at least partial remission. Moreover, the SIPS requires one or more attenuated positive symptoms to have begun or worsened in the past year, while the CAARMS requires presence in the last year but not necessarily worsening. SIPS developers considered that epidemiologic (Schultze-Lutter et al., 2014) and other (Addington et al., 2023; Brucato et al., 2021; Woods et al., 2014) evidence suggested that the worsening criterion favourably excluded large numbers of patients who were no longer at high risk of conversion/transition, while CAARMS developers considered that the SIPS unfavourably excluded large numbers of patients with a need for treatment.

Lastly, the SIPS developers preferred accordance with the DSM-5 principle of parsimony such that a second diagnosis is not needed if all of its features are accounted for by another disorder, whereas the CAARMS was often employed on its own in a clinical context and so CAARMS developers were concerned that excluding patients from a CAARMS grouping could cause them to be excluded from care. Unable to agree, the authors settled for requiring the PSYCHS to include questions that would generate both sets of CHR/UHR criteria.

The issues preventing full harmonization for the syndromes based on presence of brief fully psychotic symptoms (Table 4) were similar, as were the issues preventing full harmonization for the syndromes based on trait vulnerability and functional decline (Table 5).

3.3.1 | Modifications to CAARMS UHR criteria

With the revision of the CAARMS in 2006, CAARMS developers added functioning based on the Social and Occupational Functioning Assessment Scale (SOFAS) (Morosini et al., 2000) to the inclusion grouping criteria for the symptom-based UHR syndromes. The intention of the revision was to produce samples enriched for a higher rate of conversion to psychosis (Yung et al., 2006). Although conversion rates have been higher in some studies since the revision (van der Gaag et al., 2012), the large NEURAPRO trial incorporating the CAARMS 2006 revisions did not yield an increased conversion rate (11%, McGorry et al., 2017). This led to some subsequent CAARMS-based studies dropping the functioning requirement, which facilitated harmonizing with the SIPS on this point (Tables 3 and 4). Moreover, (1) treatment of UHR individuals may be needed in the absence of functional decline, and (2) removing the functional decline criterion would enable early intervention to prevent deterioration. However, CAARMS developers also acknowledge that the reduction in functioning criteria are widely used in health services and are valued as a means for allocating clinical resources. Maintaining the requirement for a reduction in functioning remains an option for these services, and a new version of the CAARMS will have an option to include or exclude the functioning requirement. Future PSYCHS users would also have the same option.

At the initial NIMH workshop (Addington et al., 2023), the consensus had been that the field should abandon the CAARMS

Vulnerability group/SIPS Genetic Risk and Deterioration subtype due to evidence that it was infrequent, especially in the absence of other subtypes, and did not predict onset of psychosis (Fusar-Poli, Cappucciati, Borgwardt, et al., 2016). AMP SCZ investigators, however, saw value in the subtype for the study of functional outcomes, leading to its retention. CAARMS developers agreed to base the Vulnerability group criteria on current or past schizotypal personality disorder (SPD) (First, 2014) rather than solely on current SPD (Table 5 PSYCHS CHR-P criteria based on trait vulnerability and functional impairment) after reviewing evidence that the diagnostic stability of SPD is not fully trait-like (Grilo et al., 2004). The modified CAARMS UHR criteria are included in Appendix S1.

3.3.2 | Modifications to SIPS CHR-P criteria

The SIPS has based the functional assessment requirement for Genetic Risk and Deterioration (GRD, Table 5) on the Global Assessment of Functioning (GAF) (Hall, 1995). Because of observations that GAF assessment of functioning was confounded by symptom severity (American Psychiatric Association, 1994), SIPS developers agreed to replace the GAF with the SOFAS, thus harmonizing the functional assessment scale with the CAARMS Vulnerability grouping. The modified SIPS GRD criteria are included in Appendix S1.

3.4 | Available materials

The Interviewer Manual, training and certification materials, the Screening Instrument for ascertainment and initial severity rating, and the Follow-Up Instrument for serial rating of severity, conversion/transition, and remission, are freely available for use by the research community and will become accessible on the AMP SCZ website, developed by the PREDICT DPACC in collaboration with members of ProNET and PRESCIENT with input from NIMH staff: https://www.ampscz.org. Data sharing is otherwise not applicable to this article as no datasets were generated or analyzed for the current article.

The PSYCHS will be available in an on-line REDCap version and as a printable paper copy. The on-line version adaptively skips questions made unnecessary by previous interviewer entries, provides just-in-time guidance only when needed, and automatically conducts calculations for determining psychosis and CHR/UHR criteria. Information required at follow-up to determine new onset of psychosis or CHR-P syndromes is pulled automatically from previous visits. The coding of the calculations and branching logic for the PSYCHS in REDCap was carried out by members of PREDICT DPACC and ProNET, with testing across ProNET and PRESCIENT.

3.5 | Current use

The PSYCHS is currently in use in the 42-site AMP SCZ (Brady et al., 2023) observational study (https://www.ampscz.org). As of December 2022, more than 100 interviewers had been trained and certified, more than 100 participants had undergone initial assessment, and five coordinated weekly consensus calls were ongoing. All persons gave their informed consent prior to their inclusion in the study.

4 | DISCUSSION

The principal finding of the present report is that it has been possible to harmonize the two most widely-used instruments for diagnosis and severity rating in individuals at clinical high risk for psychosis into one instrument, the PSYCHS. Full harmonization was achieved for attenuated positive symptom ratings and for psychosis diagnostic criteria, and the instrument generates modestly harmonized CHR/UHR diagnostic criteria for both CAARMS and SIPS as well as derived severity scores for both CAARMS and SIPS.

The PSYCHS can be used instead of individual SIPS or CAARMS assessment for CHR-P ascertainment and attenuated positive symptom severity rating. When used in this way, future studies ideally would permit inclusion of participants who meet criteria for either CAARMS UHR or SIPS CHR-P Progression, and sensitivity analyses in a data supplement could then report whether findings differed by CAARMS versus SIPS ascertainment or when employing CAARMS versus SIPS severity ratings. This practice would be helpful in comparing findings across studies and with meta-analysis.

4.1 | Strengths

The primary strengths of the PSYCHS are: (1) it harmonizes two instruments which both possess excellent psychometric properties, (2) the harmonization was conducted with great care by experts in both instruments, and (3) the attenuated positive symptom anchors provide detailed guidance for each of the 15 attenuated positive symptoms and are harmonized with particular attention to ensuring that anchors for each item are distinct, ordered, and graded according to similar intervals within each measurement concept. These changes are expected to yield even higher interrater reliability than already achieved with the original instruments and therefore improved signal detection. The on-line versions adaptively minimize administration time, missing data, and arithmetic errors.

4.2 | Limitations

There are also a number of limitations to the PSYCHS in its current stage of development. First and foremost is the inability of the authors to fully harmonize the CHR-P criteria across the two existing measures. Full harmonization was hampered, however, by a limited available evidence base of participants assessed using both instruments. We are aware of only one study that reports conducting independent CAARMS and SIPS interviews in the same CHR-P

participants (Kwon et al., 2012), and the report does not present diagnostic agreement or comparative predictive validity analyses. A recent study in relatives of patients with schizophrenia, however, also conducted independent interviews and reported 93% agreement, but agreement was largely due to the low prevalence of CHR-P in the sample of relatives. Of 17 cases diagnosed as CHR-P by either interview, the two interviews agreed on only 5 (29%) (Wang et al., 2022). Methods that rely on conducting only one interview and then estimating whether participants meet criteria for the other interview, while understandable in terms of limiting participant burden, may not be able to capture the other interview's assessment accurately, given the differences in the details of the data collection required.

Because of the limited database, when PSYCHS developers were faced with differences between the CAARMS and the SIPS that were difficult to resolve by compromise, there was little evidence to use as a basis for choosing one or the other. To refer to one of the critical differences in the most common CHR-P syndromes, the SIPS requires worsening of attenuated positive symptoms within the past year while the CAARMS requires presence in the last year but not necessarily worsening. Use of the PSYCHS in the AMP SCZ sample should enable analyses of this source of diagnostic disagreement and others between SIPS and CAARMS CHR-P criteria in a large sample of the same subjects, as well as comparative analyses of predictive validity. Based on these data it may be possible to fully harmonize the CAARMS and the SIPS CHR-P criteria in the future.

A second limitation derives from the harmonization of the CHR-P criteria that was possible to achieve. Although recent work suggests that the removal of the SOFAS functioning requirements from the symptom-based CAARMS inclusion groupings may not reduce the conversion rate (e.g., McGorry et al., 2017), other studies suggest that it may (e.g., van der Gaag et al., 2012). Since the SOFAS is being collected in the large AMP SCZ longitudinal observational study, the effects of applying or not applying SOFAS-based exclusion criteria can be directly tested.

A third limitation derives from the PSYCHS being a new instrument whose psychometric properties need to be established. While interrater reliability has been excellent (section 1) for both the CAARMS and the SIPS, similarly excellent inter-rater reliability for the harmonized PSYCHS cannot be assumed. We will conduct reliability studies as part of the AMP SCZ observational study, as well as criterion validity (Sheehan et al., 1998) and other psychometric studies, in accordance with guidelines from the US Food and Drug Administration (U.S. Department of Health and Human Services et al., 2022).

A fourth limitation is the synthesis of a single severity rating for each item across up to four measurement concepts. While the single severity rating has always been used for the SIPS and the CAARMS despite items including multiple measurement concepts, and could be considered a strength for assessment of outcomes, independent rating of each measurement concept may provide sufficient added value for the purposes of predicting outcome to offset the additional burden on participant and interviewer. For example, there is mixed evidence as to whether distress due to attenuated positive symptoms predicts future onset of frank psychosis independently from symptom severity (Nelson et al., 2022; Power et al., 2016; Pratt et al., 2023; Rapado-Castro et al., 2015; Rekhi et al., 2019). We plan to investigate the independent rating of each measurement concept within AMP SCZ. Regarding the synthesis of measurement concepts by the interviewers, a cognitive debriefing study may be needed to demonstrate whether interviewers understand the method of synthesis.

Another limitation is that when used to make CAARMS Vulnerability grouping/SIPS GRD determinations, the PSYCHS relies on the SOFAS (Morosini et al., 2000) for functional assessment, as well as on the Structured Clinical Interview for DSM-5 Personality Disorders (First, 2014) and the Family Interview for Genetics Studies (Maxwell, 1992) for determining presence of schizotypal personality disorder and first-degree family history of psychosis, respectively. Thus these additional instruments must be employed alongside the PSYCHS. Alternatively, schizotypal personality disorder and first-degree family history of psychosis at least could potentially be assessed using less rigorous methods.

Lastly, the PSYCHS contains 15 separate attenuated positive symptom items. While early experience in AMP SCZ indicates that administration times generally correspond to the intended 60–90 min, there have been exceptions, especially for an individual interviewer's first case or two as they gain familiarity with navigating the instrument in REDCap or RPMS. Analyses from AMP SCZ will be used to determine whether certain items could be consolidated. An important limitation of the PSYCHS is that its increased focus on positive symptoms also has required that other symptoms (including negative, disorganized, general, cognition, emotional disturbance, behavioural, motor/physical, aggression, mania, depression, suicidality, mood swing, anxiety, OCD, dissociation, and basic (Gross & Huber, 2005) symptoms) when needed must be rated using separate scales. Separate scales that are fit for these other purposes may be organized into core assessment batteries for outcome (Woods et al., 2020) and prediction.

4.3 | Summary

The Positive SYmptoms and Diagnostic Criteria for the CAARMS Harmonized with the SIPS semi-structured interview (PSYCHS) has been developed to harmonize the two most widely-used instruments for diagnosis and severity rating in patients at clinical high risk for psychosis (CHR-P). Use of the PSYCHS should facilitate comparing findings across studies in the CHR-P field.

AFFILIATIONS

[1]Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut, USA
[2]Connecticut Mental Health Center, New Haven, Connecticut, USA
[3]Division of Psychology and Mental Health, School of Health Sciences, University of Manchester, Manchester, UK
[4]Youth Mental Health Research Unit, Greater Manchester Mental Health NHS Foundation Trust, Manchester, UK
[5]Orygen, Parkville, Victoria, Australia
[6]Centre for Youth Mental Health, The University of Melbourne, Parkville, Victoria, Australia

[7]Division of Translational Research, National Institute of Mental Health, Bethesda, Maryland, USA
[8]Department of Psychiatry, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA
[9]Department of Psychiatry, Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada
[10]Department of Psychology & Neuroscience, Temple University, Philadelphia, Pennsylvania, USA
[11]Department of Psychiatry, Washington University School of Medicine, St. Louis, Missouri, USA
[12]CAMEO, Early Intervention in Psychosis Service, Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge, UK
[13]Departments of Psychiatry and Biobehavioral Sciences & Psychology, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, California, USA
[14]Feinstein Institute for Medical Research, Manhasset, New York, USA
[15]Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), CIBERSAM, ISCIII, School of Medicine, Universidad Complutense, Madrid, Spain
[16]Institute for Mental Health, School of Psychology, University of Birmingham, Birmingham, UK
[17]Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK
[18]Department of Psychiatry, University of California, San Diego, California, USA
[19]Department of Psychiatry, University of Hong Kong, Pok Fu Lam, Hong Kong
[20]Olin Neuropsychiatry Research Center, Hartford HealthCare Behavioral Health Network, Hartford, Connecticut, USA
[21]Chef de Service Service de Psychiatrie Générale Dép. de Psychiatrie CHUV Lausanne, Lausanne, Switzerland
[22]Department of Psychiatry, Donald and Barbara Zucker School of Medicine, Hempstead, New York, USA
[23]Copenhagen Research Centre for Mental Health, Mental Health Copenhagen, University of Copenhagen, Copenhagen, Denmark
[24]Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA
[25]Faculty of Medicine and University Hospital of Cologne, University of Cologne, Cologne, Germany
[26]Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA
[27]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA
[28]Department of Psychiatry and Psychotherapy, Ludwig Maximilian University Munich, Munich, Germany
[29]Department of Psychiatry and Psychotherapy, King's College London, London, UK
[30]Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
[31]Department of Psychiatry and Psychotherapy, Jena University Hospital, Jena, Germany
[32]Department of Psychiatry and Behavioral Sciences and Weill Institute for Neurosciences, University of California, San Francisco, California, USA
[33]Mental Health Service 116D, Veterans Affairs San Francisco Health Care System, San Francisco, California, USA
[34]Department of Psychology, Northwestern University, Chicago, Illinois, USA
[35]Mental Health Services in the Capital Region, Copenhagen, Denmark
[36]Department of Clinical Medicine, Copenhagen University Hospital, Copenhagen, Denmark
[37]Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA
[38]Department of Psychiatry, IMHAY, University of Chile, Santiago, Chile
[39]PEPP-Montreal, Douglas Research Centre, Montreal, Quebec, Canada
[40]Department of Psychiatry, McGill University, Montreal, Quebec, Canada
[41]Department of Psychology, University of Georgia, Athens, Georgia, USA
[42]Shanghai Mental Health Center, Shanghai Jiaotong University School of Medicine, Shanghai, China
[43]Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York, USA
[44]Department of Psychiatry, University of North Carolina, Chapel Hill, North Carolina, USA
[45]Department of Psychological Science, University of California, Irvine, California, USA
[46]Department of Medicine, Institute of Biomedical Research (IBSAL), Universidad de Salamanca, Salamanca, Spain
[47]Department of Psychosis Studies, King's College London, London, UK
[48]Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy
[49]Department of Radiology, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA
[50]Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA
[51]Department of Software Engineering and Information Technology, École de Technologie Supérieure, Université du Québec, Montréal, Quebec, Canada
[52]Institute for Mental and Physical Health and Clinical Translation, School of Medicine, Deakin University, Geelong, Victoria, Australia

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All those acknowledged have given written permission.

CONFLICT OF INTEREST STATEMENT

S.W.W. has received sponsor-initiated research funding support from Boehringer-Ingelheim, Amarex, and SyneuRx. He has been a paid consultant to Boehringer-Ingelheim, New England Research Institute, and Takeda. He has been granted US patent no. 8492418 B2 for a method of treating prodromal schizophrenia with glycine agonists. B.C.W. has been a paid consultant with Boehringer-Ingelheim and the Pier Institute. A.A. holds equity and is a member of the Technology Advisory Board for Neumora Therapeutics, Inc.; is a cofounder, serves as a member of the Board of Directors, as a scientific adviser, and holds equity in Manifest Technologies, Inc.; and is a coinventor on the following patent: Anticevic A, Murray JD, Ji JL: Systems and Methods for NeuroBehavioral Relationships in Dimensional Geometric Embedding, PCT International Application No. PCT/US2119/022110, filed Mar 13, 2019. J.M.K has received honoraria for lectures or consulting from Alkermes. R.S.K. has consulted for Alkermes, Otsuka, and Sunovion. D.O.P reports consulting for Alkermes. S.R.C. reports Speaker's Fees / Honoraria: Janssen-Cillag Australia, Lundbeck-Otsuka Australia, Servier Australia Advisory Board: Lundbeck – Otsuka Australia (Maintena, Brexpiprazole) Investigator initiated grants: Janssen-Cillag Australia, Lundbeck-Otsuka AustraliaTravel Support: Janssen-Cillag Australia. D.H.M. has served as a consultant for Neurocrine Biosciences. C.A. has been a consultant to or has received honoraria or grants from Acadia, Angelini, Biogen, Boehringer, Gedeon Richter, Janssen Cilag, Lundbeck, Medscape, Menarini, Minerva, Otsuka, Pfizer, Roche, Sage, Servier, Shire, Schering Plough, Sumitomo Dainippon Pharma, Sunovion and Takeda. E.Y.H.C. reports investigator initiated grants: Janssen-Cillag. C.M.D-C. reports grant support from Instituto de Salud Carlos III, Spanish Ministry of Science and Innovation (PI17/00481, PI20/00721, JR19/00024) and honoraria from Exeltis and Angelini. P.J.M. has received sponsor initiated funding from Alkermes, Boehringer Ingelheim, Roche, NeuroRX, and Otsuka and honorarium from Alkermes, Lundbeck, Otsuka, and BioXcel. Other authors report no conflict of interest.

DATA AVAILABILITY STATEMENT

AMP SCZ data are held in the NIMH Data Archive and available at nda.nih.gov/ampscz.

ORCID

Scott W. Woods https://orcid.org/0000-0002-3103-5228
Laura L. Adery https://orcid.org/0000-0003-0659-8309
Kelly Allott https://orcid.org/0000-0002-0640-4634
Eric Y. H. Chen https://orcid.org/0000-0002-5247-3593
Louise Birkedal Glenthøj https://orcid.org/0000-0003-3621-8450
Suzie Lavoie https://orcid.org/0000-0001-8372-2399
Covadonga Martinez Diaz-Caneja https://orcid.org/0000-0001-8538-3175
Pablo A. Gaspar https://orcid.org/0000-0002-9682-5327
Gregory P. Strauss https://orcid.org/0000-0002-7218-5169
Paolo Fusar-Poli https://orcid.org/0000-0003-3582-6788
Martha E. Shenton https://orcid.org/0000-0003-4235-7879
Monica E. Calkins https://orcid.org/0000-0002-0546-0263
Jean Addington https://orcid.org/0000-0002-8298-0756

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX A

Accelerating Medicines Partnership Schizophrenia (AMP SCZ) authors as follows:

AMP SCZ Working Group and Subgroup leaders (not previously listed): Scott R. Clark[a,b], Kathryn E. Lewandowski[c,d], John Torous[e]

National Institute of Mental Health Project Scientists: Laura M. Rowland[f], Ming Zhan[f]

Research Network and DPACC Investigators (not previously listed): Kang Ik Kevin Cho[g]

Study Coordinators and Project Managers (not previously listed): Priya Matneja[h], Christina Phassouliotis[i,j], Susan Ray[h], Callum Snowball[i,j], Jessica Spark[i,j], Sophie Tod[i,j]

[a] University of Adelaide, Discipline of Psychiatry, Adelaide, South Australia, Australia

[b] Basil Hetzel Institute, Woodville, South Australia, Australia

[c] Psychotic Disorders Division, McLean Hospital, Belmont, MA, USA

[d] Department of Psychiatry, Harvard Medical School, Boston, MA, USA

[e] Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

[f] National Institute of Mental Health, National Institutes of Health, Bethesda, MD, USA

[g] Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

[h] Northwell Health, Glen Oaks, NY, USA

[i] Orygen, Parkville, VIC, Australia

[j] Centre for Youth Mental Health, The University of Melbourne, Parkville, VIC, Australia