SYSTEMATIC REVIEW

# On the proportion of patients who experience a prodrome prior to psychosis onset: A systematic review and meta-analysis

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**BACKGROUND:** Preventing or delaying the onset of psychosis requires identification of those at risk for developing psychosis. For predictive purposes, the prodrome – a constellation of symptoms which may occur before the onset of psychosis – has been increasingly recognized as having utility. However, it is unclear what proportion of patients experience a prodrome or how this varies based on the multiple definitions used.

**METHODS:** We conducted a systematic review and meta-analysis of studies of patients with psychosis with the objective of determining the proportion of patients who experienced a prodrome prior to psychosis onset. Inclusion criteria included a consistent prodrome definition and reporting the proportion of patients who experienced a prodrome. We excluded studies of only patients with a prodrome or solely substance-induced psychosis, qualitative studies without prevalence data, conference abstracts, and case reports/case series. We searched Ovid MEDLINE, Embase (Ovid), APA PsycInfo (Ovid), Web of Science Core Collection (Clarivate), Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, APA PsycBooks (Ovid), ProQuest Dissertation & Thesis, on March 3, 2021. Studies were assessed for quality using the Critical Appraisal Checklist for Prevalence Studies. Narrative synthesis and proportion meta-analysis were used to estimate prodrome prevalence. $I^2$ and predictive interval were used to assess heterogeneity. Subgroup analyses were used to probe sources of heterogeneity. (PROSPERO ID: CRD42021239797).

**RESULTS:** Seventy-one articles were included, representing 13,774 patients. Studies varied significantly in terms of methodology and prodrome definition used. The random effects proportion meta-analysis estimate for prodrome prevalence was 78.3% (95% CI = 72.8–83.2); heterogeneity was high ($I^2$ 97.98% [95% CI = 97.71–98.22]); and the prediction interval was wide (95% PI = 0.411–0.936). There were no meaningful differences in prevalence between grouped prodrome definitions, and subgroup analyses failed to reveal a consistent source of heterogeneity.

**CONCLUSIONS:** This is the first meta-analysis on the prevalence of a prodrome prior to the onset of first episode psychosis. The majority of patients (78.3%) were found to have experienced a prodrome prior to psychosis onset. However, findings are highly heterogenous across study and no definitive source of heterogeneity was found despite extensive subgroup analyses. As most studies were retrospective in nature, recall bias likely affects these results. While the large majority of patients with psychosis experience a prodrome in some form, it is unclear if the remainder of patients experience no prodrome, or if ascertainment methods employed in the studies were not sensitive to their experiences. Given widespread investment in indicated prevention of psychosis through prospective identification and intervention during the prodrome, a resolution of this question as well as a consensus definition of the prodrome is much needed in order to effectively direct and organize services, and may be accomplished through novel, densely sampled and phenotyped prospective cohort studies that aim for representative sampling across multiple settings.

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## INTRODUCTION

Schizophrenia spectrum psychotic disorders affect close to 1% of the population globally and are significant drivers of disability and healthcare costs [1–6]. With a view to improving prognostics and early intervention, there has long been an interest in characterizing the onset and early course of psychosis – including risk,

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premorbid, and sub-threshold periods [7]. Initial investigations centering on patients who had already developed psychosis were focused on examinations of the pre-psychotic period known as the *prodrome*, which involved collection of retrospective data. In a seminal study by Hafner et al. [8], the prodrome was described as a period of symptoms (including, but not limited to, changes in affect, cognition, and social behavior) that was contiguous with the onset of psychosis: as such, a prodrome could only be retrospectively identified (once a psychosis had occurred), and was present in 73% of psychotic patients. Indeed models of illness development often indicate a number of nonspecific symptoms, negative symptoms, so-called "basic symptoms", and mood changes preceding the onset of positive psychotic symptoms (e.g. refs. [9–11]).

For researchers, the early intervention movement underscored the importance of prospectively identifying individuals at risk for developing psychosis, in order to ultimately delay or prevent its onset. Focusing on milder or "sub-threshold" versions of the characteristic symptoms of a full-blown disorder [12], prevention efforts therefore highlighted attenuated or brief intermittent psychotic symptoms such as perceptual abnormalities, subthreshold hallucinations or delusions, disorganization of speech and odd or unusual behavior [13, 14]. The resulting "clinical high-risk"(CHR; also known as the at-risk mental state [ARMS] or ultra high-risk [UHR]) state thus represents a 'putative' prodrome in which those close-in to the point of psychosis could then be prospectively followed longitudinally to determine rates and predictors of that transition [15].

Studies have now demonstrated that help-seeking individuals with these symptoms have an elevated risk of transition to psychosis for up to 10 years [16, 17]. These prospective definitions have also assisted in the development of novel service offerings: early intervention clinics, aimed at providing care to patients experiencing CHR states [16]. Work focusing on CHR has generated much excitement, demonstrating evidence of effectiveness as measured by reductions in duration of untreated psychosis, improvement of symptomatic and functional outcomes, while being cost-effective [18, 19], though there is more limited evidence for reduction of rates of CHR symptoms and of transition to psychosis [20–22].

Despite the success of work focusing on the CHR syndrome, emerging evidence regarding trajectories to psychosis has further textured our understanding of the role of the CHR syndrome and its relationship with the prodrome. First, it is now clear that the majority of CHR cases do not go on to develop psychosis, even up to 10 years following initial identification of an at-risk state [17, 23–25]. Second, although most CHR patients do not transition to psychosis, they nonetheless have high rates of developing nonpsychotic mental disorders - suggesting that 'heterotypic' shifts across diagnostic categories are frequent in this population [24, 26]; though this is not always demonstrated [27, 28]. Third, follow-back studies have now reported that in a minority of first episode psychosis cases, no identifiable pre-onset subthreshold psychotic symptoms (representing a CHR state) could be found [29, 30]. Even if such cases in fact represent a rapid onset of psychosis in which the at-risk state appears only momentarily before transitioning to FEP, this reduces (for those subjects) the period during which early identification aimed at the CHR stage might be effective.

In light of increasing research and programmatic investment in the CHR phase [31], these data highlight the need to consolidate knowledge regarding the question of what proportion of patients who develop psychosis actually experience a prior prodrome and/or prior sub-threshold positive symptoms (hereinafter referred to as the prodrome). Such information would be immediately relevant for determining the upper limit of how diagnostically-bounded CHR services alone can address the population of patients who will ultimately develop psychosis, either at present or if their reach is extended [32, 33]. Alternately, it could generate innovations in service design, delivery or integration to delay or prevent heterotypic trajectories to psychosis.

Inconsistency in measured prodrome prevalence may also be linked to changes in how the prodrome is conceptualized and captured across different research approaches (e.g. prospective versus retrospective) and definitions (e.g. broad symptoms versus sub-threshold psychotic symptoms), and might in turn inform how such definitions can be applied in the future across clinical and research settings. Better understanding of prodrome prevalence definition and variability across studies may also help to make progress in identifying differences in prodromal phenotypes - including the absence of a prodrome - which may reflect different underlying neurobiological mechanisms, the study of which may in turn yield useful biomarkers.

We therefore sought to fill this gap in the literature by conducting a systematic review and meta-analysis of studies to determine what proportion of patients experience a prodrome prior to psychosis onset. In keeping with the result of Hafner et al., we hypothesized that the majority of patients- in excess of 70%- would have a variably-defined prodrome prior to psychosis onset. We also expected the definitions of prodrome to vary considerably across the literature, and for broader definitions of the prodrome (that included more symptoms) to result in higher prodrome prevalence rates.

## METHODS

The reporting of this systematic review and meta-analysis was guided by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement. Reference [34] and was pre-registered on PROSPERO (see supplementary material for details). There were no deviations from the published protocol other than the addition of proportion meta-analysis [35] as an analytic technique.

### Research question

Our main research question was: "what proportion of patients who develop psychosis experience a prodromal phase prior to psychosis onset?" Because there have been different definitions of what a prodrome *is* over time, a secondary question was "how do the variable definitions and methods of measuring the prodrome affect the proportion of patients who experience a prodrome"? With respect to prodrome definitions, there is currently no gold-standard definition of a prodrome and we had no a priori reason to select one definition over another. We therefore adhered to the definition articulated in each study, and sought to quantify the inconsistency of results reported in the literature.

### Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) studies of first episode or subsequent episode psychosis (both affective and non-affective were included, as well as psychosis not otherwise specified) in which the prevalence of prodromal symptoms was established (whether the *primary* aim of the study or not) or (2) studies of general population cohorts followed prospectively to determine how many people experience a prodrome and eventual psychosis. In addition, studies had to (3) be studies of populations of patients, (4) provide the proportions of people who experienced a prodrome (as defined by the study) prior to onset of psychosis, and (5) apply a consistent definition of the prodrome within the study. This definition could range from specific (e.g. meeting a threshold on a specific scale) to general (e.g. a brief description of symptoms), as long as it was consistently applied.

Exclusion criteria were as follows: (1) studies in which experiencing a prodrome was an inclusion criterion as patients who developed psychosis in these cohorts would, by definition,

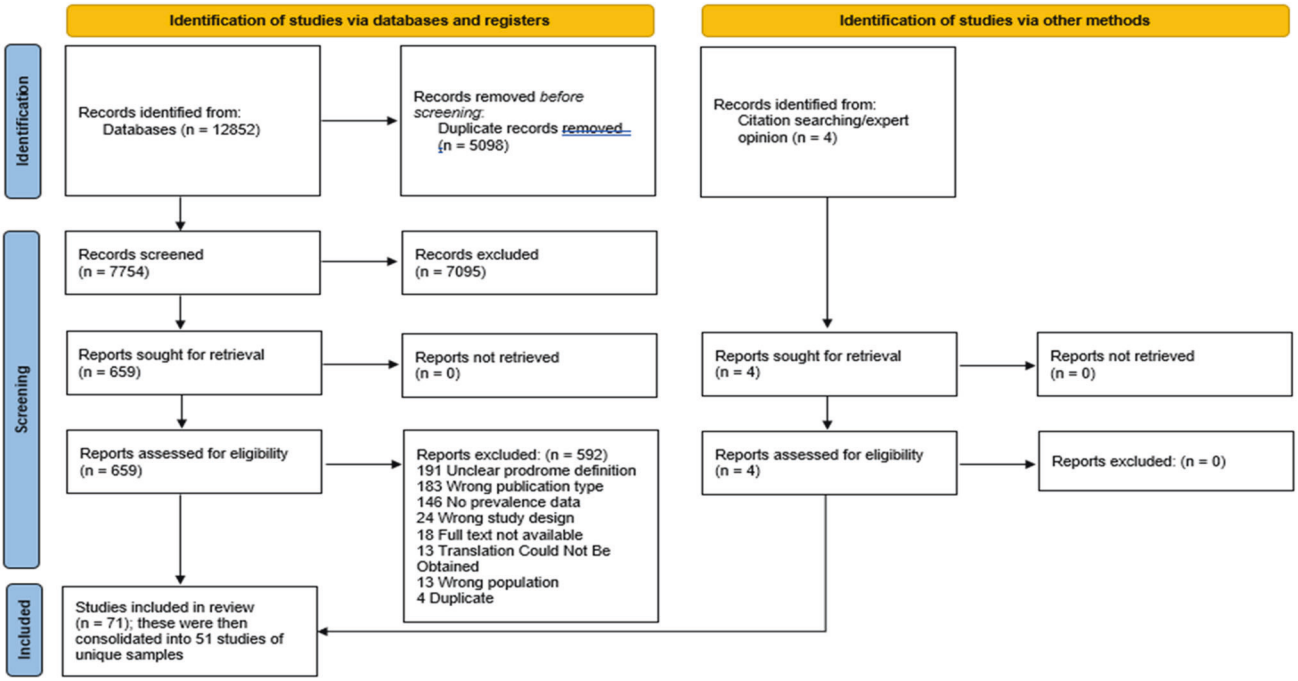


**Fig. 1 Prisma diagram for the systematic review.** Prisma diagram detailing article identification and selection and including reasons for report exclusion.

have had a preceding prodrome, artificially inflating the proportion to 100%. We also excluded (2) qualitative studies that did not report prevalence data as well as protocols, conference proceedings/abstracts, reviews, and case studies/case series; and (3) studies solely of patients with substance-induced psychosis (though studies with a minority of patients with drug-induced psychosis were allowed; it was generally not possible to separate these patients out in prevalence calculations). Further details regarding inclusion/exclusion criteria can be found in supplementary methods.

### Search strategy

On March 3, 2021 a comprehensive search was conducted using electronic databases: Ovid MEDLINE, Embase (Ovid), APA PsycInfo (Ovid), Web of Science Core Collection (Clarivate), Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, APA PsycBooks (Ovid), and ProQuest Dissertation & Thesis. No date or language filters were used. Unpublished studies, or "gray literature" (e.g. theses, program evaluation) was also included. All search strategies are presented in the supplementary material.

The final search retrieved a total of 12,852 references, which were pooled in EndNote 20 and deduplicated by the Reference Deduplicator [36]. This set was uploaded to the Covidence [37] platform for article selection. Four articles not identified by the search were added in on the advice of experts in the field. Three of these articles did not have appropriate keywords in the abstract and title [38–40] and one of them was published after our search had been conducted [41]. Given the significant amount of time required to process the articles, the decision was made not to update the search once the data extraction was complete and to defer this to an updated review in the future. A flowchart per PRISMA is presented in Fig. 1.

### Article selection

Each article was screened by title and abstract by two independent reviewers (D.B., A.C.W., V.D., P.P.); conflicts were resolved by an expert in the field (J.L.S.). Included articles were then subject to a full text review by two independent raters (D.B., A.C.W., V.D., P.P.); conflicts were resolved by group consensus at meetings including J.L.S.

### Translations and requests for missing data

For non-English articles, native speakers of the language in question with relevant expertize were sought out to assist with extraction. Speakers of English, French, Russian, Polish, and Italian were available. When these native non-English language speakers could not be found, the DEEP-L translation service (www.deepl.com) was used to provide article translations. When this translation failed or produced an unreadable article, the paper was excluded. Where further information was deemed necessary, we attempted to contact the corresponding authors of 53 articles for data or clarifications of prodrome definition and received 19 responses.

### Data extraction

Data extraction of study and patient characteristics as well as prodrome prevalence proceeded using a standardized form (available in supplementary methods). In studies which included both participants with and without psychosis, prevalence was assessed based on the total sample with psychosis. Data was extracted by one primary reviewer and this extraction was validated by a second reviewer. Conflicts in extraction were resolved via group discussion involving (D.B., V.D., A.C.W., and J.L.S.).

Once extracted, data was consolidated into a final data table, a subset of which is presented as Table 1. If several articles reported on the same sample, they were presented as a single entry in Table 1 and considered as a single datapoint reflected in the PRISMA diagram (Fig. 1).

### Assessment of article quality

Quality was assessed using the Critical Appraisal Checklist for Prevalence Studies published by the Joanna Briggs Institute (hereinafter referred to as the JBI) [42]. Because of our interest in heterogeneity, we did not exclude articles deemed to be of poor

**Table 1.** Included studies.

| Authors | Country (s) where was conducted / data collected | Years of data collection | Inclusion Criteria | Exclusion Criteria | Recruitment method | Overall quality | Recognized prodrome scale | Study setting | Sample size- | Male number/ % | Mean age and (standard deviation, if available) | Prodrome prevalence (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sandeep [92] | India | 2010–2011 | Patients 18–60 with psychotic mania | Comorbid psychiatric or significant medical or neurological illness | Admitted patients | Fair | Y | University health center (admitted patients only) | 51 | 39/76 | 24.62 | 58.82 |
| Yung & McGorry [93] | Australia | 1993 | FEP aged 16–30 | Non-psychiatric cause of psychosis, intellectual disability, active psychosis during data collection | Patients recruited from a FEP clinical service | Fair | N | University-affiliated FEP program (covering inner and Western Melbourne, sample representative of cases in that area) | 21 | 14/67 | 23.1 | 100 |
| Yildizhan et al. [94] | Turkey | 2011–2012 | FEP, age </ = 20 | Psychotic disorder due to substance use, severe congenital cognitive difficulty preventing interview, previous adequate treatment (equivalent of 6 mg haloperidol/ day for 6 weeks) | Admitted patients | Fair | Y | University health center (admitted patients only) | 43 | 32/74 | 17.38 | 100 |
| Woodberry et al. [58] | USA | NR | FEP, age 13–45, SZ spectrum | Sensory-motor handicaps, neurological disorders, medical illnesses that significantly impair neurocognitive function, intellectual disability, education less than 5th grade if under 18 or less than 9th grade if 18 or older, substance abuse in the past month, substance dependence, excluding nicotine, in the past 3 months, current suicide risk, history of electroconvulsive therapy within the prior 5 years | Recruited from area hospitals, outpatient treatment settings, and the metropolitan Boston community through advertisements, formal outreach presentations, and word of mouth | Poor | Y | University health centers, community and outpatient centers, and the metropolitan Boston area (including outreach using advertisements, outreach presentations, and word of mouth) | 40 | 27/68 | 21.9 | 95 |
| Tan & Ang [50] | Singapore | 1997–1999 | Military servicemen with FEP | Clear-cut non-psychiatric etiology for psychotic symptoms, patients with attenuated or questionable psychotic symptoms for which a firm diagnosis could not be made. | Recruited military personnel presenting with FEP to a military psychological center | Fair | N | Military psychological care center in Singapore, consecutively admitted patients | 30 | 30/100 | 20.6 | 93.33 |
| Sullivan [95] | USA | NR | SZ, male | Inadequate coupled with failure of the physician to establish satisfactory contact with the patient, intellectual disability coupled with inadequate information, questioning of the schizophrenic nature of the illness | Review of notes from the first 155 cases of SZ admitted to the study center | Poor | N | Urban hospital (first 100 patients admitted with sufficient data available to report) | 100 | 100/100 | NR | 22 |

**Table 1.** continued

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Skokou et al. [96] | Greece | 2005–2008 | Paranoid SZ, </ = 3 episodes | Subjects with non-psychiatric causes of psychiatric symptoms, or psychotic disorder due to substance use or general medical condition | Admitted patients | Fair | Y | University health center (consecutively admitted patients) in a "large administrative area of about 1 million people" | 87 | 54/62 | 30.71 ± 8.68, with a range from 17 to 59 years for males, and 36.47 ± 10.59, with a range from 21 to 65 years for females | 97.7 |
| Shioiri et al. [97] | Japan | 1999–2004 | SZ | NR | Admitted patients, chart review based on treatment records including reports by family | Fair | N | University health center | 219 | 98/45 | 33.9 | 29.68 |
| Schultze-Lutter et al. [29] [a] | Germany | NR | FEP | See GRNS | Admitted patients | Good | Y | Multicenter inpatient (16 university psychiatric departments, 14 hospitals, 6 local networks of psychiatric practice and general practitioners) | 126 | NR | 30.1 | 86.51 |
| Schothorst et al. [98] [b] | Netherlands | 1984–2000 | Aged 12–18 with diagnosis of a psychotic disorder | NR | Chart review, outpatients, inpatients, day clinic | Poor | N | University health center | 129 | 86/67 | 16.5 | 93.8 |
| Stepniak et al. [99] | Germany | NR | SZ and SZ-A | NR | Recruited as part of another study (GRAS) | Fair | N | Multicenter (GRAS; 23 centers participating throughout Germany) | 1011 | NR | NR | 81.5 |
| Salvatore et al. [100] | USA | 1989–1995 | FEP | Acute intoxication, withdrawal syndrome, delirium, previous psychiatric hospitalization, unless for detoxification, presence of intellectual disability, non-psychiatric causes of psychiatric symptoms, index syndromal illness present >6 months or previous syndromal episode, prior total treatment with an antipsychotic > 4 weeks or mood-stabilizer for >3 months | Admitted patients | Fair | Y | University health center, first episode psychosis program | 377 | 224/59 | 30.8 | 100 |
| Russell [101] | USA | NR | Up to age 13, with onset of DSM-III schizophrenia before age 11 | Intellectual disability or known neurologic or medical disorder affecting the central nervous system | Chart review screening records at one institution, followed by contacting eligible patients and their families | Poor | Y | University health center | 35 | 24/69 | 9.45 | 85.71 |

**Table 1.** continued

| Authors | Country (s) where was conducted / data collected | Years of data collection | Inclusion Criteria | Exclusion Criteria | Recruitment method | Overall quality | Recognized prodrome scale | Study setting | Sample size- | Male number/ % | Mean age and (standard deviation, if available) | Prodrome prevalence (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ropcke & Eggers [102] | Germany | 1979–1988 | SZ spectrum | Affective psychosis | Re-contacting patients after admission | Fair | Y | University health center (participants were all initially inpatients) | 39 | 20/51 | 16.9 | 35.9 |
| Shah et al. [30] [c] | Canada | 2003–2013 | FEP, age 14–35, no antipsychotic medication > 30 days | Intellectual disability, psychotic illness solely related to substance intoxication or withdrawal, or medical or neurological mental disorder. Patients with a concurrent substance use disorder were not excluded. | Patients recruited from a FEP clinical service | Good | Y | University health center, FEP program serving a catchment area | 351 | 248/71 | 23.35 | 67.81 |
| Renwick et al. [103] | Ireland | 2005–2011 | FEP, age 16–65 | Intellectual disability, psychosis due to another medical condition | Inpatients and outpatients in an early intervention in psychosis program | Good | Y | FEP Program, serving a catchment area | 375 | 219/58 | 32.9 | 80.53 |
| Perkins et al. [104] | USA | NR | Clinically stable patients with psychosis | NR | NR | Poor | Y | University health center; patients recruited from outpatient psychiatry clinics from the same center | 35 | 22/63 | 29 | 85.71 |
| Rabe-Jabllonska et al. [105] | Poland | 1984–1996 | FEP, age 15–19 | NR | Admitted patients | Good | N | University health center | 150 | 72/48 | 16.7 | 78 |
| Naqvi et al. [106] | Pakistan | NR | SZ | Comorbid substance abuse or non-psychiatric mental disorder | Convenience sampling of patients with SZ | Poor | Y | University health center | 93 | 55/59 | NR | 86.02 |
| Mustonen et al. [55] | Finland | 2001–2002 | All persons consenting from a birth cohort; national registries for diagnoses (different registries from [54]) | Psychosis diagnosis before follow-up year (< age 15–16) | Birth cohort: all live born children from the two northernmost provinces in Finland | Fair | Y | General population birth cohort and national diagnostic registries | 154 | NR | NR | 52.6 |
| Morgan et al. [63] | UK | NR | FEP, age 16–65 | Psychotic symptoms precipitated by a non-psychiatric cause, previous treatment for psychosis, transient psychotic symptoms resulting from acute intoxication | All FEP patients reporting to study clinics in 2 catchment areas | Fair | Y | Urban clinics (AESOP Study), serving 2 catchment areas in London and Nottingham | 470 | 286/61 | 30 | 79.36 |
| Moller & Husby [107] | Norway | 1994–1996 | FEP, SZ and SZ-phreniform age 18–30, no more than 2 years since first treatment | Medical illness or intellectual disability | Admitted patients | Poor | N | Urban hospital; patients were consecutively admitted | 19 | 11/58 | 22.4 | 100 |

**Table 1.** continued

| Authors | Country (s) where was conducted / data collected | Years of data collection | Inclusion Criteria | Exclusion Criteria | Recruitment method | Overall quality | Recognized prodrome scale | Study setting | Sample size- | Male number/ % | Mean age and (standard deviation, if available) | Prodrome prevalence (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Maki et al. [54] | Finland | 2001–2008 | National registry (diagnoses) and birth cohort (PROD screening): all persons who provided consent | Diagnosis of any psychiatric disorder before 2003, developmental disorders, only substance use/only non-psychiatric disorders during follow-up period | Birth cohort for Northern Finland, July 1 1985–June 30 1986; National Hospital Discharge Registry | Fair | Y | General Population Birth Cohort and Nationla Hospital Discharge Registry | 23 | 13/57 | NR | 60.87 |
| Meng et al. [108] | Switzerland, Germany, Austria | 1999–2002 | FEP, early onset | Psychopathological syndromes related to neurological or systemic disease, intellectual disability | Admitted patients | Good | Y | Multicenter, university and community sites across 3 countries (VESPA group) | 87 | 52/60 | 16.7 | 96.55 |
| Kohn et al. [109] | Germany | NR | SZ | Intellectual disability | Patients presenting to a number of clinics in a large catchment area | Fair | Y | Urban clinics in 3 cities | 82 | 60/73 | 29.8 | 89.02 |
| Kim et al. [110] | South Korea | NR | FEP, age 17–45, SZ spectrum or BAD | History of head trauma, comorbid CNS disorder, moderate to severe intellectual disability, transient psychosis after acute intoxication | Admitted patients | Poor | Y | Urban University Hospital, consecutive admissions | 20 | 11/55 | 27.1 | 90 |
| Kanahara et al. [64] | Japan | 1996–2001 | Psychosis, with no or ineffective previous treatment | Alcohol-or illicit drug-related psychosis, psychosis due to non-psychiatric causes, or psychosis due to dementia | Patients previously admitted and available at 10-year follow-up | Poor | N | Hospital serving a large catchment area | 156 | 77/49 | Not available for the whole sample. Age at onset for "severe cases at admission" 34.2 y (11.9); for "non severe cases at admission" 33.3 y, (12.3) | 73.72 |
| Jackson et al. [56] | Australia | 1986–1992 | FEP, age </= 45 | Intellectual disability, non-psychiatric causes of symptoms | Admitted patients | Fair | Y | Hospital Schizophrenia Research Unit | 313 | 196/63 | 25.5 | 60% (any 2 symptoms), 44% (DSM III definition), 25% (DSM III definition plus 6 month duration) |
| Jackson et al. [111] | Australia | NR | FEP, age 18–45 | Intellectual disability, non-psychiatric causes of symptoms | Patients recruited from a FEP clinical service | Fair | Y | University-affiliated FEP program/ Schizophrenia Research Unit; consecutive admissions | 50 | 32/64 | 26.3 | 50 |
| Iida et al. [112] | Japan | 1984–1993 | SZ, diagnosis age < 15 | NR | Patients presenting to one department of psychiatry | Fair | N | University health center | 39 | 26/67 | 14.62 | 79.49 |
| Huber et al. [113] | Germany | 1945–1959 | SZ | NR | Admitted patients | Poor | N | Patients initially admitted to an urban hospital; Patients interviewed at home or in the hospital | 502 | NR | NR | 46.81 |

**Table 1.** continued

| Authors | Country (s) where was conducted / data collected | Years of data collection | Inclusion Criteria | Exclusion Criteria | Recruitment method | Overall quality | Recognized prodrome scale | Study setting | Sample size- | Male number/ % | Mean age and (standard deviation, if available) | Prodrome prevalence (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Gourzis et al. [114] | Greece | 1992–1997 | SZ | NR | All patients admitted to the only inpatient service in a catchment area | Fair | Y | University health center, serving a large catchment area | 100 | 64/64 | 25.6 | 100 |
| Gottlieb [115] | USA | 1929–1933 | First admission patients with hebephrenic SZ, with a high school education and who were natively urban | No "physical defects" | Admitted patients | Poor | N | Urban Hospital | 100 | NR | NR | 100 |
| Creel [116] | USA | NR | SZ or SZ-phreniform service members | NR | Random sample from eligible patients in the US Armed Forces | Fair | N | US Armed Forces | 40 | 34/85 | 22.5 | 75 |
| Costello [57] | USA | 2001–2010 | SZ with at least one related hospital admission or four related outpatient appointments | Schizophrenia cases that remained in active service for more than two years aft er meeting the surveillance case definition were assumed to have been misdiagnosed and removed from analysis. Individuals who were considered incident cases of schizophrenia in 2001 were excluded from analyses if they received any schizophrenia diagnoses during the year 2000. | Review of all relevant US Armed Forces records | Fair | N | US Armed Forces | 3000 | 2578/86 | age at dx: 17–24, 60%; 25–29, 24%; 30–34, 10%; 35 + 7% | 71 |
| Coryell & Zimmerman [117] | USA | NR | Psychosis (delusions, hallucinations, formal thought disorder) | Current mania, medical or drug history which might invalidate the dexamethasone suppression or thyrotropin releasing hormone test | Admitted patients | Poor | Y | University health center, serving a large catchment area | 21 | 9/43 | 33.4 | 66.67 |
| Conus et al. [118] | Australia | 1998–2000 | FEP | Non-psychotic diagnosis, transferred away from study clinical service | Chart review at a FEP service | Fair | N | University-affiliated FEP program covering a catchment area (north-west and western suburbs of Melbourne) | 597 | 435/73 | 22 | 80.57 |
| Chen et al. [119] | UK | 2005–2016 | FEP, age 16–45, no antipsychotic medication 1 year prior to FEP diagnosis, registered for 5 years at a participating practice | Parkinson's disease or dementia in the 5 years prior to FEP, record of psychosis in remission 5 years prior to analysis | National registry of 10 million patients registered with over 670 primary care practices | Fair | N | 568 Primary care practice contributing to a primary care record database | 3045 | 1914/63 | median (IQR): 30 (23, 39) | 51.17 |
| Chen et al. [120] | Hong Kong (China) | 1997–2000 | FEP | Previous psychotic episode, known neurological condition, history of special school attendance (proxy for moderate to severe learning disability). | All patients presenting to public facilities in the catchment area | Fair | Y | Urban public healthcare facilities covering a catchment area in Hong Kong | 131 | 58/44 | 31.5 | 72.52 |

**Table 1.** continued

| Authors | Country (s) where was conducted / data collected | Years of data collection | Inclusion Criteria | Exclusion Criteria | Recruitment method | Overall quality | Recognized prodrome scale | Study setting | Sample size- | Male number/ % | Mean age and (standard deviation, if available) | Prodrome prevalence (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day et al. [121] | Denmark; India; Colombia; USA; Nigeria; Japan; Czechoslovakia | NR | First psychosis contact, SZ-spectrum diagnosis, onset of florid psychotic symptoms within 7 days, onset of illness occured within 6 months of screening data for study, onset can be dated reliably to within one week's time | NR | NR | Fair | N | Multicenter, urban and rural WHO field research centers serving catchment areas but with varying case-finding networks | 386 | 198/51 | percentage given for each center, see paper if needed. majority under 30; tables 6.1 and 6.2 | 33.42 |
| Bensi et al. [122] | Italy, UK | 2006–2007 | SZ-spectrum (non-affective), delusional disorder, psychosis NOS, with relapse leading to readmission | NR | Admitted patients | Fair | N | Urban hospital | 253 | 174/69 | 48.8 | 65.22 |
| Dominguez-Martinez et al. [51] | Spain | NR | FEP, age 14–40 | NR | Patients recruited from a FEP clinical service | Fair | Y | FEP Program | 40 | 25/63 | 26 | 85 |
| Bechdolf et al. [123] | Germany | NR | SZ, either first episode or relapse from remission; remitting from symptoms at time of evaluation | NR | Admitted patients | Fair | Y | Urban Psychiatric clinic | 33 | 18/54 | 20 | 96.97 |
| Addington et al. [124] | Canada | NR | SZ-spectrum, < 3 months adequate treatment once admitted to the study service, completed 1 year followup | NR | Patients recruited from a FEP clinical service | Fair | Y | University-affiliated FEP program, serving a catchment area in Calgary (however only considered subjects who completed a one-year followup) | 86 | 57/66 | 24 | 84.88 |
| Barajas et al. [125] | Spain | NR | 2 or more psychotic symptoms, age 12–45, initial contact with mental health services within the previous 6 months, < 1 year since onset of psychiatric symptoms | Intellectual disability, head injury, dementia or any non-psychiatric causes of psychosis, low verbal IQ (IQ < 85) | Recruited from adult, child and adolescent community and hospital mental health services in a metropolitan area and outskirts | Poor | Y | Hospitals and community psychiatric services in the metropolitan area and outskirts of Barcelona | 79 | 44/56 | 20.22 | 100 |
| Varsamis & Adamson [38] | Canada | NR | FEP-SZ | NR | Admitted patients | Poor | N | Hospital, urban; consecutive admissions | 44 | 27/61 | median 31.5 | 75 |
| Hafner et al. [53, 126] [d] | Germany | 1987–1989 | First admission for psychosis, diagnosed with SZ broadly, age 12–59 | First admissions age 0–11, non-psychiatric cause of psychosis, severe intellectual disability | Admitted patients, representing 84% of first admissions in the catchment area | Fair | Y | Multisite, urban and rural; covering a catchment area | 232 | 108/47 | 30.3 | 73.28 |

**Table 1.** continued

| Authors | Country (s) where was conducted / data collected | Years of data collection | Inclusion Criteria | Exclusion Criteria | Recruitment method | Overall quality | Recognized prodrome scale | Study setting | Sample size- | Male number/ % | Mean age and (standard deviation, if available) | Prodrome prevalence (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Comptom et al. [127, 128] [e] | USA | 2004–2008 | Psychosis (non-affective), recent onset or previously untreated, age 18–40, MMSE >/ = 23 | Intellectual disability, significant medical condition affecting participation, prior antipsychotic treatment of >3 months, hospitalization for psychosis >3 months prior to index hospitalization | Admitted patients in two public-sector hospitals and an urban county psychiatric crisis center | Fair | Y | Urban, university-affiliated, public-sector hospital and urban county psychiatric crisis center | 109 | 83/76 | 23 | 69.72 |
| Eggers & Bunk [129] [f] | Germany | 1925–1961 | Childhood onset schizophrenia, onset age 7–14 | NR | Admitted patients | Fair | Y | University health center; all admissions during the time period were screened | 57 | NR | NR | 54.39 |
| Guloksuz et al. [130] | Netherlands | 2007–2016 | Random sample | NR | Random sample | Good | Y | General population sample | 26 | NR | NR | 38.46 |
| Ferrara et al. [17] | USA | 2014–2019 | Subjects for this analysis were drawn from consecutive admissions to a community health center-based FES (Specialized Treatment Early in Psychosis, STEP) over 5 years (February 1st, 2014, to January 31st, 2019). STEP's broad eligibility criteria includes between the ages 16–35 who were within the frst 3 years of psychosis onset, and also met Structured Clinical Interview for DSM-IV TR diagnosis for any non-organic schizophrenia-spectrum or schizoafective psychosis, including schizophreniform disorders, brief psychotic episode, and psychosis NOS. Services were also restricted to residents in a ten town catchments contiguous with the clinic in New Haven, Connecticut. | The clinic excluded referrals with an established diagnosis of afective psychosis (Bipolar Disorder and Major Depressive Disorder with psychotic features), and psychosis secondary to substance use or a medical illness. | Subjects for this analysis were drawn from consecutive admissions to a community health center-based FES (Specialized Treatment Early in Psychosis, STEP) over 5 years (February 1st, 2014, to January 31st, 2019). For most of this period, STEP hosted an early detection campaign that sought to recruit a representative sample across the catchment area [21]. | Good | Y | Community, but university affiliated FEP clinic; catchment area of ten towns near New Haven | 168 | 118/70 | 22.4 (3.8) | 88.1 |

[a]Studies include: Schultze-Lutter et al. [131], Schultze-Lutter et al. [29].
[b]Studies include Schothorst et al. [98], Emck et al. [132].
[c]Studies include: Shah et al. [30], Pierre [133], Iyer et al. [134], Cupo et al. [11].
[d]Studies include: Hafner [135], Maurer et al. [136], Hafner et al. [137], Hafner et al. [138], Hafner [126], Hafner [139], Häfner et al. [138].
[e]Studies include Compton et al. [127], Compton et al. [60], Compton et al. [140], Compton et al. [141], Compton et al. [128].
[f]Studies include Eggers & Bunk [129], Eggers & Bunk [142], Eggers et al. [143], Eggers [144], Eggers et al. [143].

quality: instead of the JBI checklist item asking the reviewer to decide to include or exclude the article, we modified the scale by asking each reviewer to independently rate the article as being of "good", "fair" or "poor" quality based on their overall assessment of the checklist criteria. To conservatively estimate study quality, the lower of the two reviewers' ratings was assigned to the article.

### Grouping for analyses

The primary analysis of prodrome prevalence and literature heterogeneity ($I^2$ and prediction interval; [43, 44]) included all selected and extracted studies. We also report the prediction interval (the interval in which the prevalence estimate from the next hypothetical study to be added to the metanalysis is expected to lie) for the prevalence of prodrome to supplement our estimate of heterogeneity [44, 45]. Subgroup analyses are recommended in proportion meta-analysis, as they can assist in the determination of sources of heterogeneity [44]. To determine potential sources of heterogeneity in the primary analyses and to assess the impact of measurement approaches, study population selection, or methodology on prodrome prevalence, further estimates of $I^2$, prediction interval and prevalence were performed on the following subgroups as secondary and exploratory analyses: only those studies rated as being "fair" or "good" on quality assessment; only those studies conducted within first episode psychosis clinics; only those studies conducted using patient interviews; only those studies deriving estimates from self report; only those studies conducted on a population or catchment area sample; only those studies conducted using chart review; studies which included solely inpatients; studies with definitions inspired by the Interview for the Retrospective Assessment of the Onset of Schizophrenia (IRAOS; a detailed symptom-based measure) [46]; studies with definitions inspired by the DSM-III [47] (which is syndromal in nature as opposed to being focused on individual symptoms); studies including only patients with schizophrenia spectrum disorders; studies including patients with more heterogeneous diagnoses (e.g. including affective psychosis and delusional disorder and other psychotic disorders); only those studies which sought to assess prevalence of prodromal symptomatology; and only those studies which used a validated prodrome scale. In cases where a study's membership in a subgroup was unclear, it was assumed not to be part of the subgroup.

### Meta-analysis

For our primary aim of determining the prevalence of prodrome prior to psychosis onset, a meta-analysis of reported proportions was conducted. We used random effects models given the expected inconsistency between studies in terms of results and methodology and we present the results as a forest plot. Meta-analyses were carried out using MedCalc v20.2 (MedCalc Software Ltd.). Heterogeneity (the variation in estimates between studies, whether in primary or subgroup analyses) was assessed using the $I^2$ metric [43] as well as the prediction interval. The prediction interval, which assesses the interval within which a new point estimate would lie based on the studies in the meta-analysis, and which provides another estimate of data variability with clinical relevance (based knowledge of what would constitute clinically relevant uncertainty), was calculated using Comprehensive Meta-Analysis Version 4 [44, 48].

### Publication bias

The presence of publication bias was assessed using the Begg's test and funnel plot [49]. Given the relative lack of commercial interests in this specific field, we did not expect there to be significant publication bias.

### Categorizing prodrome definitions

We grouped prodrome definitions into three categories as follows. The first was the "Non-specific" group, which consisted of those studies which had brief or underspecified definitions; for example one study in this category defined the prodrome as a "disturbance or deviation from the patient's previous experience and behavior that occurs before the development of florid psychotic features" [50]; these may have, but did not always, include attenuated psychotic symptoms. A further example of the "Non-specific" group would be the study by [51], who defined the onset of the prodrome as "the earliest clinically significant deviation from the patient's premorbid personality… established considering the first appearance of either attenuated positive or negative symptoms". This was judged as being non-specific because any number of symptoms could be considered as fulfilling these criteria.

The second group was the "Attenuated Psychotic Symptoms Only" or "APS Only" group; this group defined the prodrome solely on the basis of sub-threshold psychotic symptoms such as perceptual changes or the onset of bizarre thoughts (e.g. [30], where the focus was on 9 expert-defined sub-threshold psychotic symptoms; or [41] where the symptoms were defined based on the Structured Interview for Psychosis-Risk Syndromes (SIPS) assessment [52]).

The third group was the "Specified Broad" group. This group considered explicit lists of symptoms or diagnoses (as opposed to the "Non-specific" group) which were broader than (but could nonetheless include) APS. An example of the "Specified Broad" category would be the [53] study, in which a specific instrument (the IRAOS) was used to establish the presence of a number of specified symptoms. These groups are presented in Table 2.

Further exploratory analyses were conducted to assess the impact of changing definitions over time and regions on prevalence rates and are presented in the supplementary material.

## RESULTS

### Articles selected

Results of the article selection process are demonstrated in the PRISMA flow diagram (Fig. 1). The search resulted in 12,852 articles. After removal of duplicates, 7758 studies were screened. 663 relevant studies were assessed as full texts, of which 592 were excluded, leaving 71 articles in the review. The three most common reasons for exclusion were: unclear (or missing) definition of the prodrome which did not allow us to assess what the authors meant by the prodrome; ineligible type of publication (e.g. a conference abstract); or article did not contain prodrome prevalence data. Note that a given article may have had multiple reasons for exclusion, but only one reason for exclusion, based on a structured and ordered list agreed by the extraction team, was recorded per article. After merging articles which reflected identical samples ([54, 55] were kept separate, despite being conducted on the same birth cohort, as different diagnostic databases were used, identifying different numbers of patients), our final dataset for this review included 51 studies.

Included studies are described in Table 1. Twenty-one studies (41.2%) were conducted in Europe; 15 (29.4%) in North America; 9 (17.6%) in Asia; 4 (7.8%) in Oceania; and 2 (3.9%) were conducted in multiple countries. These regions are of course not homogeneous with respect to language, ethnicity, culture, medical practices, and a host of other variables, but are grouped to facilitate analysis. There were no studies from South America or Africa. The majority of studies were conducted at specialty clinics, university-affiliated sites, hospitals, or within urban areas, indicating a lack of representation from community and rural sites; this is counterbalanced by other large studies examining large population samples and primary care/community clinics.

For the 44 studies that reported detailed sex or gender data, the average percentage of a sample that was male was 64% (SD = 0.13). All but 4 studies were published after 1980, the year the DSM-3 was released [47].

With respect to quality, 30 (58.8%) studies were of "Fair" quality, 7 (13.7%) of "Good" quality, and 14 (27.5%) of "Poor" quality.

**Table 2.** Prodrome definitions: studies and sample sizes.

| Type of prodrome definition | Author(s) | Sample size | Total |
|---|---|---|---|
| Non-specific | Yildizhan et al. [94] | 43 | 2132 |
| | Tan & Ang [50] | 30 | |
| | Sullivan [95] | 100 | |
| | Russell [101] | 35 | |
| | Ropcke & Eggers [102] | 39 | |
| | Rabe-Jabllonska et al. [105] | 150 | |
| | Naqvi et al. [106] | 93 | |
| | Morgan et al. [63] | 470 | |
| | Moller & Husby [107] | 19 | |
| | Kohn et al. [109] | 82 | |
| | Kanahara et al. [64] | 156 | |
| | Creel [116] | 40 | |
| | Coryell & Zimmerman [117] | 21 | |
| | Conus et al. [118] | 597 | |
| | Chen et al. [120] | 131 | |
| | Dominguez-Martinez et al. [51] | 40 | |
| | Addington et al. [124] | 86 | |
| Specified broad | Sandeep [92] | 51 | 10,823 |
| | Yung & McGorry [93] | 21 | |
| | Skokou et al. [96] | 87 | |
| | Shioiri et al. [97] | 219 | |
| | Schultze-Lutter et al. [29] | 126 | |
| | Schothorst et al. [98] | 129 | |
| | Stepniak et al. [99] | 1011 | |
| | Salvatore et al. [100] | 377 | |
| | Renwick et al. [103] | 375 | |
| | Perkins et al. [104] | 35 | |
| | Mustonen et al. [55] | 154 | |
| | Maki et al. [54] | 23 | |
| | Meng et al. [108] | 87 | |
| | Kim et al. [110] | 20 | |
| | Jackson et al. [56] | 313 | |
| | Jackson et al. [111] | 50 | |
| | Iida et al. [112] | 39 | |
| | Huber et al. [113] | 502 | |
| | Gourzis et al. [114] | 100 | |
| | Gottlieb [115] | 100 | |
| | Costello [57] | 3000 | |
| | Chen et al. [119] | 3045 | |
| | Day et al. [121] | 386 | |
| | Bensi et al. [122] | 253 | |
| | Bechdolf et al. [123] | 33 | |
| | Barajas et al. [125] | 79 | |
| | Varsamis & Adamson [38] | 44 | |
| | Hafner et al. [53, 126] | 232 | |
| | Compton et al. [127, 128] | 109 | |
| | Eggers & Bunk [129] | 57 | |
| Attenuated (or subthreshold) Psychotic symptoms | Woodberry et al. [58] | 40 | 585 |
| | Shah et al. [30] | 351 | |
| | Guloksuz et al. [130] | 26 | |
| | Ferrara et al. [41] | 168 | |

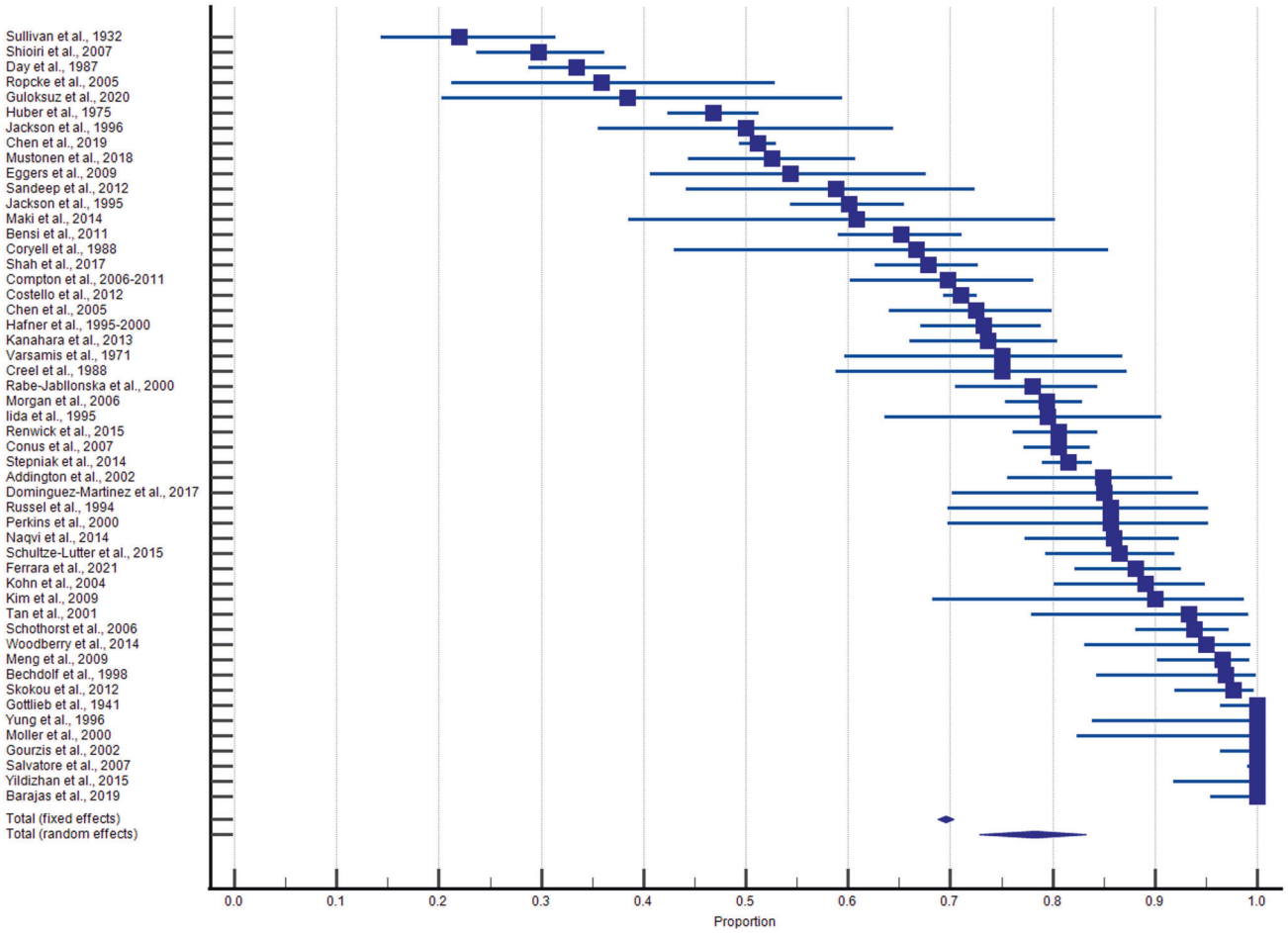


**Fig. 2 Forest plot for all studies.** Studies with publication year are listed on the Y axis and prevalence is listed on the X axis. Both fixed and random effects meta-analysis results are included for completeness.

Methodologically, 19 (37.3%) of studies did not use a validated prodrome scale; 41 (80.4%) of studies included some form of interview with the patient; 6 (11.8%) relied solely on chart review (one of these used administrative diagnosis data rather than the chart itself); and 3 (5.9%) relied solely on self-report (i.e. questionnaires completed by patients). Forty-eight (94.1%) studies determined the presence of the prodrome in a retrospective fashion (i.e. follow-back analyses after psychosis onset, relying on patient and family recall or on documentation available from before onset). There were two clearly prospective study, [54] and [55], where patients from a birth cohort were administered a prodrome screening questionnaire during one time interval and were then followed to determine whether they developed psychotic symptoms during a later time interval using different national registries in Finland. We note that the lack of prospective studies is not surprising, given that most prospective studies of prodrome use prodromal symptoms to include patients, and this would have led to these studies being excluded as we did not include studies of solely patients with prodromal symptoms.

Eighteen (35.3%) of the studies were catchment-based or population-level studies. With respect to setting, 24 (47%) of studies recruited only inpatients and 9 (17.6%) were conducted at first episode psychosis/first episode schizophrenia clinics. The most common diagnoses (Table 1) were schizophrenia and schizophrenia spectrum disorders.

## Prodrome prevalence

The combined sample size of the included studies was 13,774 patients with psychosis. The primary outcome of this review is an estimate of the prevalence of the prodrome prior to psychosis onset. Note that for one study [56] the authors offered several prevalences according to varying definitions; we selected the definition that produced the highest prevalence for the purposes of the meta-analysis. The results are demonstrated in the forest plot Fig. 2 and the funnel plot in Fig. 3 (full weights per study are available in the supplementary results).

The random effects meta-analysis estimate of the prodrome prevalence is 78.3% (95% CI = 72.8–83.2): included studies found that 78.3% of patients with psychosis experienced a pre-onset prodrome of one definition or another. The $I^2$ for this analysis is 97.98% (95% CI = 97.71–98.22), demonstrating high inconsistency. The prediction interval was wide (95% PI = 0.411–0.936). Consistent with the funnel plot, there was a low risk of publication bias on Begg's test (Kendall's Tau= 0.015; $p = 0.88$).

## Prodrome definitions

There was relatively little variation in prodrome prevalence across definition categories, contrary to our initial hypothesis. Seventeen (33.3%) of the studies fell into the "Non-specific" definition category; these studies had a mean prevalence of 76.9% (SD = 20.4%). Four studies (7.8%) fell into the "APS only" definition category; these studies had a mean prevalence of 72.3% (SD = 25.4%). Thirty (58.8%) studies fell into the "Specified Broad" category; these had a mean prevalence of 74.5% (SD = 21.2%). We included in this latter category the study by Costello [57] which focused on administrative data, since the authors specified that any preceding mental health diagnoses would be considered to be prodromal. Final groupings based on definition can be found in Table 2.

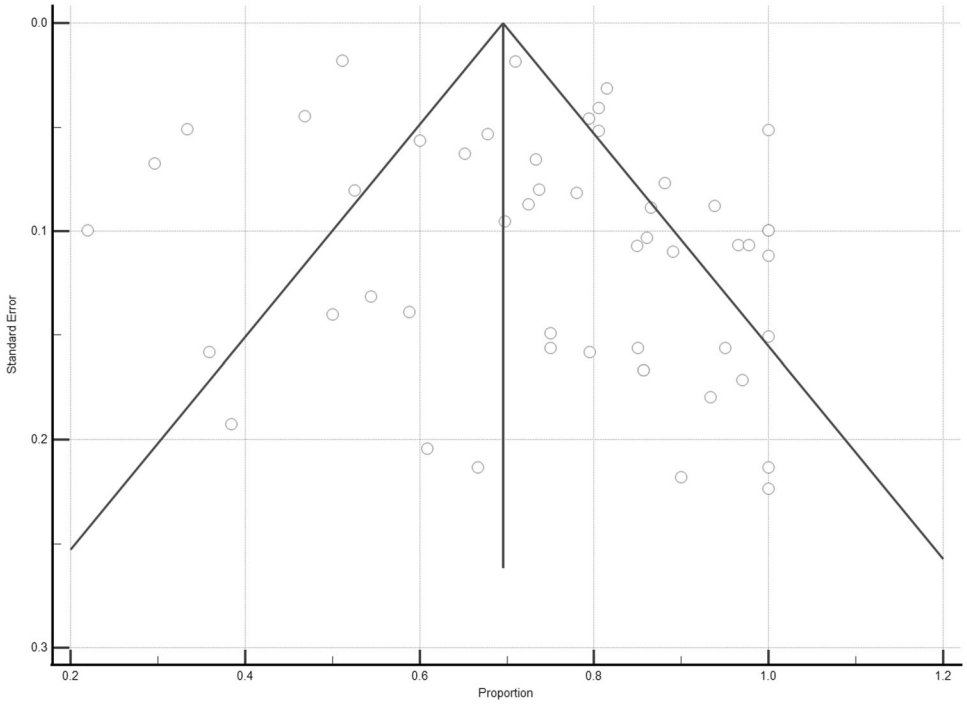


**Fig. 3 Funnel plot for all studies.** Funnel plot for assessment of publication bias.

### Prodrome prevalence - subgroup analyses

Given the high inconsistency present in the estimate of prodrome prevalence derived from all the studies, we conducted multiple post-hoc subgroup analyses aimed at identifying potential sources of heterogeneity. These results are presented in Table 3. No subgroups demonstrated publication bias (Begg's test $p$'s all > 0.05).

As can be seen in Table 3, the majority of the subgroups had point estimates close to the overall estimate of 78.3%. Nonetheless, the individual estimates from each subgroup have high heterogeneity and wide prediction intervals. Even when the purpose, or one of the main purposes, of the study was to assess prodromal symptom prevalence, the prediction interval was wide. More intensive data gathering methodologies (e.g. interviews, using a prodrome scale) and the use of validated instruments did tend to generate higher prodrome prevalence than studies with less intensive methodologies (e.g. chart review, self-report). Overall, however, studies generated similar estimates even when using different definitions, or when using instruments with different approaches to determining if the prodrome had been present (e.g. the DSM-III vs. the IRAOS).

Furthermore, with the exception of self report, the degree of inconsistency within each subgroup remained extremely high in all subgroups. We note that the estimates for the two studies using the SIPS assessment were relatively close: 88.1% in [41] and 95% in [58], but the inconsistency within the APS group is high when including all APS-definition studies. The FEP service-only subgroup yielded an estimate close to the group average; as such, the shorter recall times theoretically afforded by focusing on FEP patients does not appreciably affect the estimate. Finally, the small self-report subgroup has both a much lower estimate of the prevalence (54.8%) as well as a much lower inconsistency (0%) compared to both the analysis including all data as well as every other subgroup; however, this inconsistency had a wide confidence interval, indicating that the $I^2$ estimate for this subgroup (which contains only four studies) is uncertain. Predictive intervals in the subgroups were also generally wide.

## DISCUSSION

This is the first systematic review and meta-analysis to determine what proportion of patients experience a prodromal phase prior to onset of threshold-level psychosis. Our results confirm the results of previous work (Table 1) that a prodrome is experienced by a substantial majority of patients who develop psychosis. Our overall estimate is a prevalence of 78.3%, though individual studies have reported prevalences as low as 22% and as high as 100% - representing high heterogeneity ($I^2$ 97.98% [95% CI = 97.71–98.22]) and a wide prediction interval (95% PI = 0.411–0.936). There were no meaningful differences in prevalence between grouped prodrome definitions, and subgroup analyses failed to reveal a consistent source of heterogeneity. Implicit in the question of how frequently the prodrome occurs before psychosis, however, are two assumptions that deserve to be examined: first, that a variably-defined pre-psychotic period (e.g. nonspecific prodrome, CHR/ARMS state, etc…) exists in a large number of patients with psychosis; and second, that these states can be accurately and reliably identified and measured using current methodologies. Our results seem to support the first assumption (i.e. that a large proportion of patients experience a prodrome). Indeed, the observation that disparate methodologies tend to generate similar estimates might increase our confidence in the general finding that the *majority* of patients experience a prodrome. However, the possibility that even a minority (21.7%) of patients experience no prodrome raises questions about measurement approaches, the underlying concepts being appraised and captured, and implications for the structure and function of next-generation services.

### Are there truly patients who do not experience a prodrome?

A clear possibility is that a sizeable minority of patients experience a rapid change from a state of relative wellness to florid psychosis, without an intermediate period of nonspecific or sub-threshold symptoms - akin to previous observations of "acute" (vs. "insidious") onset of psychosis [59–63]. This subgroup has clinical relevance because it is thought to have a better prognosis [62, 64], suggesting potentially different neurobiological mechanisms or

**Table 3.** Meta-analysis results for subgroups.

| Subgroup | Number of studies included | Sample size (total patients) | Prodrome prevalence estimate (Random Effects) | Prodrome prevalence estimate 95% CI | $I^2$ | $I^2$ 95% CI | 95% Predictive interval |
|---|---|---|---|---|---|---|---|
| Only "good" or "fair" quality studies | 37 | 12401 | 76.4% | 70.1–82% | 98.2% | 97.9–98.4% | 39.7–92.8% |
| Only studies conducted at FES/FEP services | 9 | 2001 | 78.1% | 70.2–85% | 92.9% | 88.7–95.5% | 44.1–93.4% |
| Only self-report from patients | 3 | 228 | 54.8% | 48.3–61.1% | 0% | 0–92.8% | Not calculated;between study variance estimated at 0 |
| Only studies which conducted interviews | 41 | 6535 | 80.3% | 73.7–86.2% | 97.5% | 97.1–97.8% | 38.4–95.9% |
| Studies which used the DSM-III | 5 | 585 | 81.1% | 46.5–99.4% | 98.5% | 97.8–99% | 4.8–99.8% |
| Studies which used the IRAOS | 8 | 868 | 81.4% | 70.1–90.5% | 93.5% | 89.5–96% | 37.4–96.4% |
| Only studies of large populations or involving catchment areas | 18 | 9069 | 77.7% | 70.5–84.1% | 97.9% | 97.4–98.3% | 43.2–92.4% |
| Only studies which used a prodrome scale | 32 | 3933 | 80.6% | 73.3–87.0% | 96.6% | 95.9–97.2% | 41.8–95.5% |
| Only studies which did not use a prodrome scale | 19 | 9841 | 73.1% | 64.6–80.8% | 98.5% | 98.2–98.8% | 31.5–92.4% |
| Only studies of inpatients | 24 | 3238 | 78.6% | 66.9–88.3% | 98.2% | 97.8–98.5% | 32.8–95.4% |
| Only studies using solely chart review | 6 | 6971 | 74.2% | 59.4–86.6% | 99.2% | 98.9–99.4% | 22.1–95.6% |
| Only studies including mixed diagnosis samples | 23 | 6880 | 77.7% | 67.9–86.1% | 98.6% | 98.3–98.8% | 36–94.2% |
| Only studies including schizophrenia spectrum samples | 28 | 6894 | 78.7% | 72.1–84.7% | 97% | 96.3–97.5% | 40.7–94.5% |
| Only studies using the APS only definition | 4 | 585 | 75.4% | 56–90.6% | 94.6% | 89.3–97.3% | 2.7–99.7% |
| Only studies using the Non-specific definition | 17 | 2132 | 78.6% | 70.8–85.4% | 93.4% | 90.8–95.2% | 39.7–94.7% |
| Only studies using the Specified Broad Definition | 30 | 11057 | 78.4% | 70.9–85.1% | 98.6% | 98.4–98.8% | 39.9–93.2% |
| Only studies which sought to assess prodrome prevalence as a primary aim | 22 | 8742 | 72.14% | 64.4–79.3% | 97.9% | 97.4–98.3% | 33.2–91.5% |

developmental pathways underlying both their onset of illness, and perhaps the illness itself. Identifying these differences in clinical trajectory and neurobiology may ultimately lead to improved or tailored treatments for this and other subgroups. Additionally, because these patients' putatively rapid transition to psychosis leaves little opportunity for them to be identified by CHR or general/nonspecific early-intervention services during the prodrome, services would need to be alert to this group and have intake mechanisms geared towards rapid diagnosis, assessment and treatment. An alternative is that this subgroup *does* in fact experience a prodrome, but simply one that is more challenging to measure or that is not captured by the majority of current assessment methodologies, for example because of difficulties in recalling prodromal symptoms (the vast majority of studies considered here relied on retrospective recall or records), or because the prodrome they experience is qualitatively different to the prodrome captured by most current methods. One important point to consider, particularly in light of retrospective data collection approaches, is that of the subtle differences and potential interplay between experiences such as pre-morbid adjustment and prodromal symptoms. Without a clear definition of the prodrome, it may be a challenge to effectively separate poor pre-morbid adjustment from symptoms of a prodrome. In the effort to make this separation, it is possible that some patients who did in fact have a prodrome were ascertained to instead have poor pre-morbid adjustment, leading to an undercount of prodrome incidence in some studies. The opposite is also potentially true: some patients who had poor pre-morbid adjustment may have been counted as having prodromal symptoms. Further exploration of the nature of pre-morbid adjustment and how this intersects with, and/or can be differentiated from, the prodromal period should be an important part of future prospective studies.

In summary, it is possible that a sizeable minority of patients do not experience a recognizable prodrome, but it is at least equally plausible that all patients experience a form of prodrome that for some is difficult to recall, transient, or challenging to identify or measure. Clarity on which of these alternatives is the case (and if so, on what form the prodrome (or prodromes) not reliably measured by current methods takes) would provide critical knowledge to inform the breadth of feasible targets for psychosis prevention. The importance of this question for the structure and function of mental health services is not in doubt [31, 65]; however, resolving it requires that the field achieve a consensus definition of the prodrome, operationalizes it in a manner that can be consistently applied, and then generates prospective data from a range of settings which can then be compiled.

### Is the APS definition adequate?

There is currently a great deal of clinical and research effort aimed at determining how to best provide care for, and predict transition to psychosis amongst, patients who meet the criteria for a clinical high-risk state [17, 24]. The main focus in these settings continues to be on sub-threshold psychotic symptoms, commonly defined by the type and intensity of brief or attenuated positive symptoms present [66]. It is striking, however, to note that the vast majority of the literature on the prodromes experienced by patients who actually develop psychosis do not appear to focus solely on subthreshold positive symptoms of psychosis or APS. Rather, the prodrome has frequently been appreciated as inclusive of a range of affective, negative, positive, non-specific, basic, cognitive, and other symptoms. However, given the more specific definition of the prodrome contained in APS-only studies, it is perhaps surprising that these seem to yield similar estimates of prodrome prevalence, rather than meaningfully lower estimates as one might assume due to their less expansive symptom criteria. In support of this assumption, there are indeed higher prodrome prevalences (close to 100%) when broader definitions (including symptoms beyond the APS definition) are applied to identical datasets [11, 30]. Nonetheless, all three definition subgroups are within 5% of each other's estimates and lie within each other's confidence intervals. Such findings suggest that most patients who eventually develop psychosis will at some earlier point experience APS, even if their initial symptoms are nonpsychotic ones [30].

If APS are a relatively late-stage symptom cluster, occurring after changes in mood, cognition, social function, and other prodromal symptoms [11, 53, 67], then are APS-only definitions of prodrome sufficient? With the ultimate objective being to identify patients and intervene early in order to maximize clinical benefit, interventions relying on APS-based definitions may overlook opportunities to identify or delay the onset of psychosis. Indeed, APS-specific interventions may have relatively limited effectiveness even with respect to reducing APS symptoms or transition rates for patients at the CHR stage [20, 21]. As such, while APS may be a necessary and important part of an eventual gold-standard prodrome definition, they may not be adequate, especially when taking heterotypic trajectories into account. Recent work on initiatives such as HiTOP, clinical staging, and p-factor theory [68–71] have all suggested that illness development occurs in a pluripotential and transdiagnostic manner, prompting a better appreciation of the heterotypy inherent in the risk, onset and course of mental illnesses. Our findings, and recommendations below, are consistent with this understanding of illness development and the need to develop services accordingly.

### Prevalence and heterogeneity

Because the $I^2$ is a poor measure of heterogeneity in proportion meta-analyses, the use of prediction intervals and subgroup analyses is strongly recommended [44]. Our prediction interval runs from 41.1 to 93.6%, demonstrating the large heterogeneity in estimates of rates of prodrome between studies in the main analysis. Per subgroup analyses, high heterogeneity (in terms of both I2 and PI) persists even when attempting to group studies by the instruments used, setting, or the methodological approach. While there is some degree of variability across these subgroups (likely due in part to their substantial overlap), the differences between the estimates produced are relatively modest in comparison to the heterogeneity within each subgroup; this along with overlapping confidence intervals makes interpreting these differences challenging.

The fact that the large inconsistency between study estimates persists even when subgrouping studies suggests that the inconsistency is not clearly attributable to differences in specific constructs or methodologies, but that it may instead draw on differing conceptualizations or operationalized definitions of the prodrome as well as differing research practices. This should underscore the extent to which improved uniformity of assessment of the prodrome in practice will be critical to obtaining clarity on the question of prodrome prevalence, with corresponding implications for our mechanistic understanding of psychosis onset, treatment development, and service delivery.

### Strengths and limitations

This is, to our knowledge, the first systematic review of prodrome proportion conducted. Strengths include the incorporation of studies in multiple languages in recognition of the many ways in which the prodrome has been operationalized globally, and the fact that we integrated various definitions of the prodrome while also disaggregating them in subgroup analyses. These subgroup analyses also examined potential sources of heterogeneity. The high $I^2$ values reported here are common for prevalence meta-analyses, especially with large numbers of studies, and limit our ability to interpret the $I^2$. In this case, we followed the recommendation of [44] who suggested conducting sensitivity

analyses (including subgroup analyses) and reporting prediction intervals to better examine heterogeneity.

The most significant limitation in this review is the substantial heterogeneity across studies. Despite concerted attempts via prodrome category or subgroup analyses, we were unable to identify clear explanations for this. This suggests that the estimates we have identified should be interpreted with caution, and there may be unidentified variables that account for this inconsistency. It also implies that there are meaningful differences between the ways in which different research groups carry out their work that cannot be explained by broad methodological choices, and which are in turn inherently linked to the absence of standard definition of, technique for the measurement of, or lack of consensus in conceptualizing the prodrome. The lack of complementary measures (such as validated biomarkers) which could reduce ambiguity in clinical measurement and therefore potentially improve the reliability of the results presented here, is also a challenge to overcome.

Second, our review yielded few prospective studies in which prodrome definitions could be tested with respect to their predictive validity. Instead, the vast majority of studies identified relied on retrospective definitions of the prodrome, and as such on the recall of patients or the accuracy of medical records not created with the documentation of the prodrome in mind. Despite our subgroup results suggesting that studies with theoretically shorter recall periods (FEP clinic studies) do not differ meaningfully from those with potentially longer recall periods, some degree of recall bias may remain in the reported proportions. Researchers may have employed differing skills or effort levels when soliciting retrospective data from patients, families, or medical records - an unmeasured but potential source of heterogeneity that can only be accounted for in future prospective studies, as we will discuss below.

Third, we note the lack of data on prodrome prevalence from South America, Africa, and Asia (including the Middle East). Cultural differences in the experience and conceptualization of psychiatric symptoms have long been recognized, which means that the findings from this review may not reflect or be directly generalizable to these jurisdictions. It is, however, reassuring to note that there were no meaningful differences in prodrome prevalence rates by the regions we could include, which does suggest some conserved phenomenology (see the supplementary material).

Fourth, the sample considered here is majority male; while this is not inconsistent with the demographics noted in first episode programs (see Table 1), women tend to have different ages and patterns to psychosis onset [53, 72–76] and so future efforts may need to focus on understanding gender differences in the prodrome as well.

Fifth, we note the lack of differences in prodrome point estimates between the three prodrome definitions. Part of this may be explained by the overlap between groups, and this may limit our ability to interpret this finding. For example, the majority of studies representing the non-specific and specified broad groups would have included APS as part of their definitions. However, it is striking that the non-specific definitions produced similar estimates as those studies with well-operationalized definitions.

Finally, the primary question (and its focus on prodrome prevalence) relied on the prodrome being "absent" or "present". This may have reduced the resolution of the data available and precluded an analysis of the prodrome as a spectrum of symptoms and severities. This was necessary, however, in order to generate a metric which could be compared between studies, given the inconsistency in definitions between them.

### Recommendations for the field

The persistent heterogeneity across our analyses prompts us to recommend a concerted effort to generate both a consensus definition of the prodrome, as well as a validated and universal procedure for measuring and prospectively sampling it. Only through a large-scale, multi-site and multi-country prospective study recruiting population-based samples [77] can it be determined what proportion of individuals who develop psychosis do experience a prior prodrome (and what form or forms this takes). A prospective design with standardized and reproducible assessment methodology can enable a comprehensive range of potential prodromal symptoms to be captured while minimizing variations in researcher efforts and practices.

In addition to standardization and reproducibility, any such study would require broadly scoped, longitudinal, and temporally dense sampling of participants over an extended period of time. While the definition of the prodrome based on symptoms alone has launched and enabled decades of productive research and the development of novel clinical infrastructures, our results suggest that revised definitions of the prodrome should be inclusive of additional dimensions beyond symptoms alone in order to have predictive validity, which can then be used to direct services and assist in the development of novel treatments. As such, novel techniques which can be implemented at scale should be used to provide augmenting measures which may be clinically meaningful [78, 79]. These would include computerized cognitive batteries (e.g. [80]), performance on both existing and novel computational tasks (e.g. [81–83]; Vercammen, Aleman [79, 84]), and potentially digital phenotyping [85] and biomarkers [86–89]. These extra measures may, for example, help differentiate the cognitive changes seen in a patient with depression from those indicative of an incipient psychosis. Data from this cohort would allow different prodrome definitions to be tested and selected based on (a) predictive validity in terms of predicting psychosis onset and (b) the capacity to differentiate patients who will develop psychosis from those who will develop other mental health conditions.

Such a study would undoubtedly require immense cost and effort, but would nonetheless be worthwhile. Almost by definition, prevention or delay of early psychosis requires an understanding of what proportion of patients experience a prodrome and the form this takes. Ninety years of research - the majority of it retrospective in nature - has been unsuccessful in this endeavor, indicating the need for a concerted and prospective attempt with prospective approaches, inclusive of but not restricted to subthreshold psychotic symptoms.

Crucially, the conduct of this study in a prospective manner as described above would enable creation not necessarily of a single unitary 'prodrome' but rather of a staged definition [68, 90], potentially with subgroups with distinct progression trajectories (including the possibility of a subgroup with no or very short prodromal periods). This staged definition would allow for the development of screening instruments or interventions best suited (in both form and intensity) to a specific stage. As a potential example of this consistent with current conceptualizations, a two stage definition might consist of an "early" prodrome corresponding to nonspecific symptoms, and a "late" prodrome in which subthreshold psychotic symptoms have emerged [91]. The addition of novel measurement modalities (e.g. biomarkers, computational tests) may also add to the staging model as some of these measures may change in concert with, or ideally predict, changes in stage and these may in turn contribute to both screening efforts and treatment targets in the future. Overall, having a valid definition would allow the field to improve screening processes, and potentially to introduce screening at scale that could determine if there are some patients who will simply not develop a prodrome, and to plan services accordingly. Most importantly, it would allow further mechanistic research on individuals in "true" prodromal states (however defined) which, in turn, could allow us to develop novel treatments that could delay- or perhaps prevent- the onset of psychosis.

## CONCLUSIONS

In this systematic review and meta-analysis, we present for the first time an estimate of the prevalence of prodrome prior to psychosis onset across nearly 90 years of research. Our estimate of 78.3%, while comprehensive, reveals a high degree of heterogeneity which largely remained even when subgrouping studies based on definitions of prodrome or on methodologies, and which was associated with a wide predictive interval. We argue that a way forward is a large-scale, prospective, densely and representatively sampled cohort study using both rigorous symptom assessments and cognitive, behavioral, and computational batteries that could generate gold-standard prodrome definition(s). The findings of such a study would serve to strengthen and focus world-wide efforts to delay or prevent the onset of psychosis.

## DATA AVAILABILITY

Analyses were carried out using commercially available software. Data required to reproduce analyses are included in Tables 1 and 2.

## CODE AVAILABILITY

Analyses were carried out using commercially available software. Data required to reproduce analyses are included in Tables 1 and 2.

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## AUTHOR CONTRIBUTIONS

DB contributed to study conceptualization and the study protocol, data collection, conducted the data analysis, and led manuscript writing and revisions. VD, ACW, and PP contributed to study conceptualization and the study protocol, data collection, manuscript writing. MCF contributed to study conceptualization, prepared the search strategy, and contributed to manuscript writing. MF, ARP III, SWW, SG, ARY and VS contributed to study conceptualization, advised on analyses, and contributed to manuscript writing and revision. JS provided supervision, contributed to study conceptualization and the study protocol, advised on the data analysis, and contributed to manuscript writing and revisions.

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## COMPETING INTERESTS

The authors declare no competing interests.

## ADDITIONAL INFORMATION

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