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Sensitivity of the clinical high-risk and familial high-risk approaches for psychotic disorders – a systematic review and meta-analysis

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Review Article

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Abstract

Background: Psychosis prediction has been a key focus of psychiatry research for over 20 years. The two dominant approaches to identifying psychosis risk have been the clinical high-risk (CHR) and the familial high-risk (FHR) approaches. To date, the real-world sensitivity of these approaches – that is, the proportion of all future psychotic disorders in the population that they identify – has not been systematically reviewed.

Methods: We systematically reviewed and meta-analysed studies in MEDLINE, Embase, PsychINFO, and Web of Science (from inception until September 2024) that reported data on the sensitivity of CHR and FHR approaches – i.e., individuals with a psychosis diagnosis preceded by a CHR diagnosis or a history of parental psychosis (PROSPERO: CRD42024542268).

Results: We identified four CHR studies and four FHR studies reporting relevant data. The pooled estimate of the sensitivity of the CHR approach was 6.7% (95% CI: 1.5–15.0%) and of the FHR approach was 6.5% (95% CI: 4.4–8.9%). There was a high level of heterogeneity between studies. Most FHR studies had a low risk of bias, but most CHR studies had a high risk of bias.

Conclusion: Pooled data suggest that CHR and FHR approaches, each, capture only about 6–7% of future psychotic disorders. These findings demonstrate the need for additional approaches to identify risk for psychosis.

Introduction

Psychotic disorders, such as schizophrenia, are characterised by hallucinations, delusions, diminished emotional expression, low motivation, and disorganized speech and behaviour (American Psychiatric Association, 2013; World Health Organization, 1992). They typically have an onset in late adolescence and early adulthood and are frequently chronic with high levels of disability (Díaz-Caneja et al., 2015; Olin & Mednick, 1996). Early detection and intervention for psychotic disorders is known to improve outcomes (Correll et al., 2018).

A major focus of psychiatric research over the past two decades has been to move beyond detection in the early stages of psychosis and to identify people at risk of psychosis before the onset of illness (Fusar-Poli et al., 2020). To date, there have been two dominant approaches to psychosis prediction and prevention research: the clinical high-risk (CHR) approach and the familial high-risk (FHR) approach to psychosis.

The CHR approach – also known as the at-risk mental state (ARMS) or the ultra-high-risk (UHR) approach – usually involves identifying individuals at risk of psychosis based on the presence of one or more of the following criteria: (1) attenuated psychotic symptoms, (2) frank yet brief and intermittent psychotic symptoms, and (3) first-degree-relative of someone with psychosis coupled with a marked functional decline in the past year (Fusar-Poli et al., 2013; Yung & Nelson, 2013).

A systematic review of CHR studies found that 29% of individuals meeting CHR criteria transitioned to psychotic disorders in the following two years (Fusar-Poli et al., 2012), although there is considerable variation in transition rates between studies depending on the specific CHR criteria applied, the length of the follow-up period, and the population from which recruitment occurred (Conrad et al., 2017; Fusar-Poli et al., 2012; Malla et al., 2018; Schultze-Lutter et al., 2015a; Welsh & Tiffin, 2014).

The FHR approach, on the other hand, involves identifying individuals at risk for psychosis based solely on having one or more relatives (especially first-degree relatives) with a history of

psychotic disorder (Fusar-Poli et al., 2021). Individuals meeting FHR criteria are at an increased risk of developing psychotic disorders (Agerbo et al., 2015; Rasic, Hajek, Alda, & Uher, 2014; Uher et al., 2023), with a recent systematic review finding an absolute lifetime psychosis risk of 8% among offspring who had parents with a history of psychotic disorder (Uher et al., 2023).

While it is well-established that individuals meeting CHR or FHR criteria have an increased risk of future psychosis, only recently have researchers begun to assess the sensitivity of these approaches for capturing psychosis risk. That is, what proportion of future psychosis diagnoses in the population are captured by the CHR and the FHR approaches. This is important because it informs us about the upper limit of psychosis cases that could be prevented using these approaches if we had an effective preventive intervention (Kelleher, 2023; Lång et al., 2022). We aimed to systematically review and meta-analyse studies that reported data on the proportion of future psychosis cases captured by the CHR or the FHR approach.

Methods

Search strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) framework (Page et al., 2021) to structure this review. We ruled out a pre-existing review or review protocol on International Prospective Register of Systematic Reviews (PROSPERO) (Booth et al., 2011). Two authors (AT and IKG) searched for published articles on MEDLINE, Embase, PsychINFO and Web of Science (core collection) (from their inception till September 2024). The search was carried out in the full-text field with variations of following keywords: "psychosis," "schizophrenia," "at-risk mental state," "ultra-high risk," "clinical high risk," and "familial high risk." We also used Medical Subject Headings (MeSH) around "psychosis" and "schizophrenia spectrum disorder" on MEDLINE, Embase, and PsychINFO. The search strategy (Supplement 1) was developed in consultation with subject-matter experts (IK, CH, UL, and KOH) in the research team and a research librarian.

Eligibility criteria

Peer-reviewed and published studies meeting the following criteria were included: (a) the study population being the general population or, in the case of CHR studies, the population attending CHR services, (b) studies reporting the incidence or prevalence of psychosis diagnoses and the proportion of psychosis diagnoses that were preceded by a CHR diagnosis or a family history of psychosis; (c) CHR status assessed through either the Comprehensive Assessment of at Risk Mental States (CAARMS) (Yung et al., 2005) or the Structured Interview for Psychosis Risk Syndromes (SIPS) (T. J. Miller et al., 2003); (d) FHR status assessed in terms of any history of diagnosed psychotic disorder among one or both parents.

Studies were excluded when they met any of the following criteria: commentaries, letters, conference abstracts, editorials, study proposals/protocols, and case studies.

In terms of the CHR approach, we wished to assess real-world sensitivity. That is, looking at populations with existing CHR services, we wished to identify the total proportion of psychotic disorders identified in CHR clinics in those populations. There were other studies that calculated the sensitivity of the CHR approach within specific, highly selected (i.e., biased) samples (Fusar-Poli et al., 2016; Koutsouleris et al., 2021; Papmeyer et al., 2018; Peralta et al., 2019; Schultze-Lutter, Klosterkötter, & Ruhrmann, 2014; Schultze-Lutter et al., 2015b; Schultze-Lutter, Schimmelmann, & Michel, 2021; Schultze-Lutter et al., 2022; Yung et al., 2008, 2006). As these studies do not tell us about the real-world sensitivity of CHR services, and are not generalisable to the population, they were not included in our meta-analysis.

Screening and extraction

All search results were exported to and de-duplicated on Covidence ('Covidence Systematic Review Software', 2024). AT and IKG independently screened the articles against the eligibility criteria, specifying the reason for any exclusion. Studies not identified by the main search but known to the authors were also included. Any disagreements between AT and IKG were discussed with KOH, IK, UL, or CH to reach consensus. AT and IKG extracted data independently on Covidence. The following data were extracted: (a) the study design, (b) demographic characteristics, (c) psychosis diagnostic criteria based on the International Classification of Diseases (ICD) or the Diagnostic and Statistical Manual of Mental Disorders (DSM) codes, (d) instruments used to ascertain CHR and FHR statuses, and (e) data concerning the sensitivity of CHR and FHR approaches.

Risk of bias assessment

AT and IKG independently appraised the included studies for the risk of bias using a modified version of the Newcastle-Ottawa Quality Assessment Form for Cohort Studies (Wells et al., 2021). The following aspects were assessed in relation to the 'selection' and the 'outcome' domains of the tool: (a) representativeness of the exposed cohort (i.e., subjects with CHR/FHR), (b) selection of the non-exposed cohort (i.e., subjects with no CHR/FHR), (c) ascertainment of exposure (i.e., CHR/FHR status) and outcome (i.e., psychosis status among index subjects), (d) adequacy of follow-up time (i.e., for how long the subjects were followed up for the psychosis outcome), and (e) follow-up response rate.

The possible scores range from 0 to 7. We graded the studies in following categories based on their domain-specific score (Wells et al., 2021): (a) 'low risk' for a score of 3 or 4 in selection domain AND 2 or 3 in outcome domain, (b) 'moderate risk' for a score of 2 in selection domain AND 2 or 3 stars in outcome domain, and (c) 'high risk' for a score or 0 or 1 in selection domain OR 0 or 1 in outcome domain (Supplement 2).

Statistical analysis

Estimating the sensitivity of CHR and FHR

We meta-analysed the sensitivity proportions to present pooled sensitivity point estimates, along with 95% confidence intervals [CI]) calculated using Wilson's Score method (Newcombe, 1998), for CHR and FHR separately using Stata/SE 18 ('*meta*' package). We employed a random-effects model assuming that different studies estimated different (yet related) sensitivity estimands, since the assumption of one true estimand may not hold for prevalence or proportion data (Munn, Moola, Lisy, Riitano, & Tufanaru, 2015).

The raw proportions were transformed using the Freeman-Tukey double-arcsine transformation approach to improve their statistical properties (Barendregt, Doi, Lee, Norman, & Vos, 2013; Freeman & Tukey, 1950). To weigh each study, we used the inversed variance of each transformed proportion of that respective study (Borenstein, Hedges, Higgins, & Rothstein, 2010), following

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the Sidik-Jonkman approach (Deeks, Higgins, & Altman, 2019; Sidik & Jonkman, 2002). The pooled estimates were then back-transformed to proportions (J. J. Miller, 1978) and presented with forest plots.

Assessing heterogeneity

We investigated the evidence of heterogeneity in the pooled estimates across studies, i.e., – whether the variation across studies exceeds that expected from random error alone – by computing Cochran's χ^2 test statistic (Cochran, 1954) and the corresponding p-value. We considered a p-value of <0.10 as statistically significant evidence of heterogeneity (Deeks et al., 2019).

We quantified statistical heterogeneity through the I^2 statistic; i.e., the proportion of the variability that is attributable to heterogeneity rather than to random error (Higgins & Thompson, 2002). We also presented the τ^2 statistic which represents the variance of the distribution of the underlying estimands across studies (Borenstein et al., 2010), and the H^2 statistic, which represents the ratio of the observed variance to the expected variance from random error alone (Higgins & Thompson, 2002).

Analyses of sub-groups

When a study was deemed markedly heterogenous in terms of pre-specified characteristics, e.g., CHR/FHR assessment criteria or the risk of bias, we excluded it from the overall meta-analysis and performed a sub-group meta-analysis. The exclusion was considered influential if the sub-group and the overall estimates had non-overlapping CIs (Deeks et al., 2019).

Registration of the protocol

The protocol was registered on PROSPERO (Booth et al., 2011) on 10th May 2024 (registration number: CRD42024542268).

Findings

Selecting eligible studies

The electronic database search retrieved 9,130 unique articles. We also added three studies (Blomström et al., 2016; Debost et al., 2019; Mortensen, Pedersen, & Pedersen, 2010) following expert consultation within the research team. We excluded 9,103 articles after title and abstract screening and 23 after full-text screening. During the full-text screening, the study by Ajnakina et al. (2017) (Ajnakina et al., 2017) was excluded, since it involved a sub-set of one of the samples studied by Fusar-Poli et al. (2017) (Fusar-Poli et al., 2017). Also, since Burke et al. (2022) reported data relating to both CHR and FHR (Burke et al., 2022), we excluded the FHR sample since it involved a help-seeking population referred to a CHR service as opposed to a general population with data on familial risk. One study that experts had identified as possibly relevant was not included as it was ultimately not possible to calculate FHR sensitivity from the available data. This resulted in five eligible studies from our database search (Burke et al., 2022; Fusar-Poli et al., 2017; Healy et al., 2024; Sullivan et al., 2020; Veijola et al., 2013) and two eligible studies from expert consultation (Blomström et al., 2016; Debost et al., 2019). Therefore, in total, we included seven studies (Blomström et al., 2016; Burke et al., 2022; Debost et al., 2019; Fusar-Poli et al., 2017; Healy et al., 2024; Sullivan et al., 2020; Veijola et al., 2013) in the review.

Of the seven included studies, three (Burke et al., 2022; Fusar-Poli et al., 2017; Sullivan et al., 2020) reported data on the sensitivity of the CHR approach, involving four unique samples. Fusar-Poli et al. (2017) reported sensitivity data from two mutually exclusive populations in South London: one from the Lambeth and Southwark boroughs (denoted in this review as Fusar-Poli et al., 2017 *(a)*) and the other from the Croydon and Lewisham boroughs (denoted in this review as Fusar-Poli et al., 2017 *(b)*).

We identified one study that reported on the sensitivity of the FHR approach (Healy et al., 2024). We also identified three additional studies, however, from which it was possible to extract data on FHR sensitivity (Blomström et al., 2016; Debost et al., 2019; Veijola et al., 2013) (Figure 1).

Description of included studies

Baseline characteristics

Six out of the seven included studies were conducted in Northern Europe (United Kingdom (Fusar-Poli et al., 2017; Sullivan et al., 2020), Sweden (Blomström et al., 2016), Finland (Healy et al., 2024; Veijola et al., 2013) and Denmark (Debost et al., 2019)) and one in Australia (Burke et al., 2022). While three of the four FHR studies were based on total population-wide registries (Blomström et al., 2016; Debost et al., 2019; Healy et al., 2024), one of the three CHR studies was based on primary data from a total population-wide cohort (Sullivan et al., 2020), whereas the other two were based on help-seeking populations (Burke et al., 2022; Fusar-Poli et al., 2017).

Characteristics of CHR studies

The CHR status was assessed with the CAARMS instrument in two studies (Burke et al., 2022; Fusar-Poli et al., 2012). Sullivan et al. (2020), on the other hand, assessed psychosis-like symptoms through a semi-structured questionnaire, referred as Psychosis-Like-Symptoms Interview (PLIKS); the assessment was then matched to the SIPS criteria, to determine the CHR status at age 18. Regarding psychosis diagnostic criteria, Fusar-Poli et al. (2017) reported ICD-10 codes to ascertain all psychosis diagnoses, whereas Burke et al. (2022) used the DSM-IV criteria to determine all psychosis diagnoses. Sullivan et al. (2020) compared the PLIKS assessment with SIPS-psychosis and CAARMS-psychosis criteria to determine the presence of psychosis. The age of individuals when CHR was determined was 18 years, on average, in two of three CHR studies (Burke et al., 2022; Sullivan et al., 2020), while the other study did not report it (Fusar-Poli et al., 2017) (Table 1).

Characteristics of FHR studies

We identified one study that reported on the sensitivity of the FHR approach (Healy et al., 2024). We also identified three additional studies from which it was possible to extract data on FHR sensitivity (Blomström et al., 2016; Debost et al., 2019; Veijola et al., 2013). All four studies (Blomström et al., 2016; Debost et al., 2019; Healy et al., 2024; Veijola et al., 2013) defined FHR as any individual with a parental history of a psychotic disorder. However, the studies used different age intervals to assess and assign the FHR status among the offspring. Healy et al. (2024) determined FHR in the offspring at different age cut-offs: at birth, at 5th birthday, at 13th birthday, at 18th birthday, and at any time between their birth and the end of the follow-up period (25–29 years of age). Debost et al. (2019) determined FHR from birth till 15 years of age . Blomström et al. (2016) ascertained FHR between 13 and 33 years of age. Veijola et al. (2013) ascertained FHR from birth till 20 years of age. Three of the four FHR studies reported non-affective psychosis diagnoses as the

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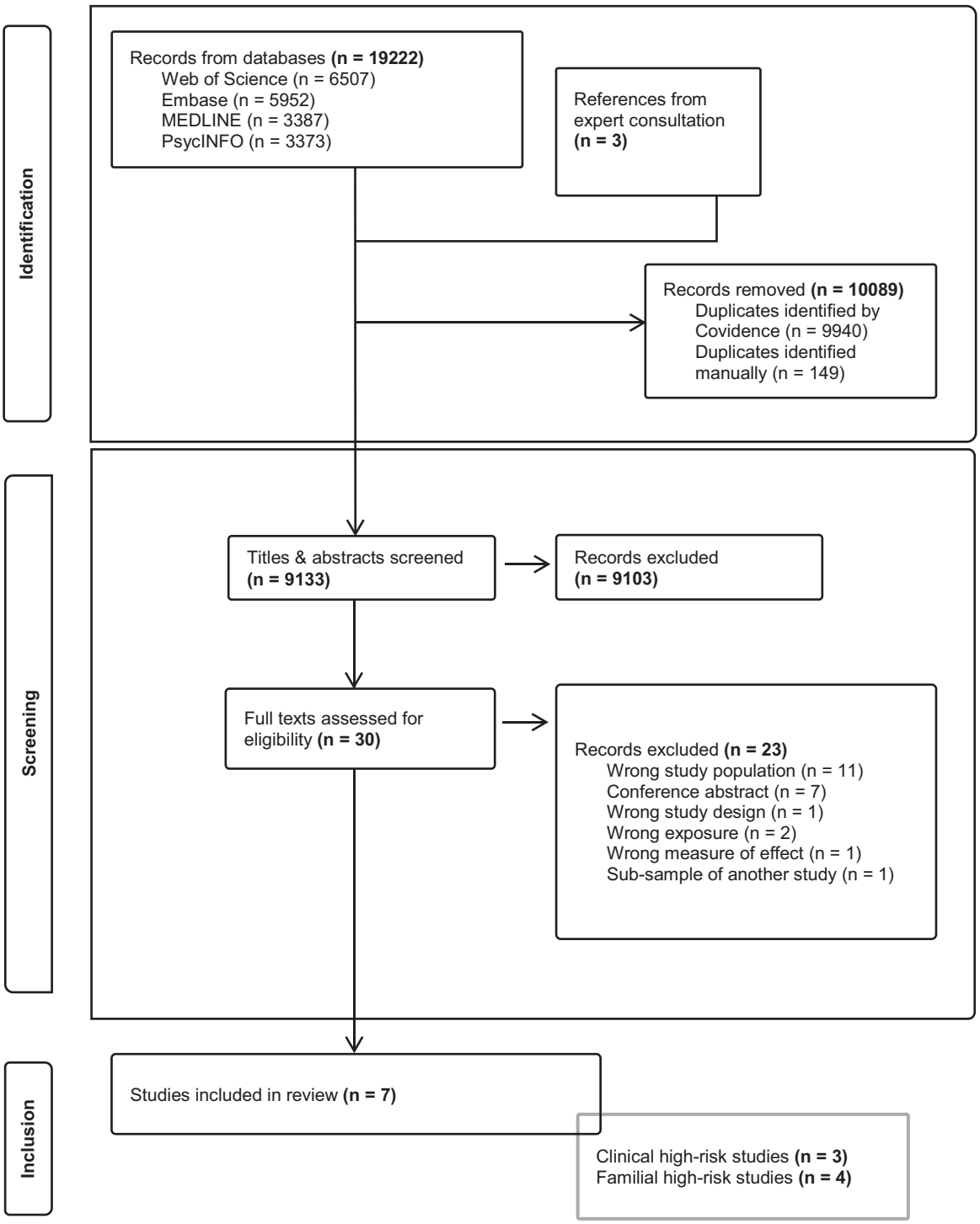

Figure 1. PRISMA flow diagram of the study selection process.

outcome (Blomström et al., 2016; Debost et al., 2019; Healy et al., 2024) (Table 2).

Risk of bias in included studies

Two of the three CHR studies (Burke et al., 2022; Fusar-Poli et al., 2017), were found to be at high risk of bias, because their participants were not representative of the average CHR individuals in the community, they may not have performed an independent blind assessment of the outcome (i.e., psychosis), and they did not report the retention rate or whether the retention was adequate at the end of the follow-up. The third CHR study (Sullivan et al., 2020), on the other hand, had a low risk of bias (Supplement 3).

Three of the four FHR studies were found to have a low risk of bias (Blomström et al., 2016; Debost et al., 2019; Healy et al., 2024). The fourth study (Veijola et al., 2013) had a moderate risk of bias since their retention proportion was less than 50%, implying a risk that the participants were non-representative of typical FHR cases in the community. In addition, it was not possible to rule out the

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Table 1. Characteristics of clinical high-risk studies

	Fusar-Poli et al. (2017)	Sullivan et al. (2020)	Burke et al. (2022)
Study setting	Help-seeking population visiting SLaM clinic, London, UK	General population in Avon, UK (birth cohort 1991–92)	Help-seeking population visiting Orygen clinic, Melbourne, Australia
Total sample (n)	(a) 33,830, (b) 54,716*	2,804	1,123
CHR assessment			
Period when assessed	2008–2015	2009–2010	2012–2016
Age (years)	Not reported	At 18	Mean (SD): 18 ± 2.8
Assessment tool	CAARMS	PLIKS (matched to SIPS criteria)	CAARMS
Psychosis diagnosis			
Period when assessed	(a) 1589 days (b) 1588 days (on average, after CHR assessment)*	2009–2015	2–3 years after CHR assessment**
Age (years)	Not reported	18–24	Mean (SD): 19.4 ± 2.8
Assessment tool	CAARMS	PLIKS (matched to SIPS and CAARMS criteria)	CAARMS
Nature of diagnosis	Non-affective psychosis, psychotic disorders due to psychoactive substance use, affective psychosis, bipolar affective disorder with psychotic symptoms, depression with psychotic symptoms	Psychotic disorder defined as a regular occurance of psychotic experience, reported as very distressing or with a very negative impact on social or occupational functioning or leading to professional help-seeking	Schizophrenia, schizophreniform disorder, drug-induced psychosis, psychosis not otherwise specified, not differentiated, brief psychotic disorder, delusional disorder, schizoaffective and bipolar affective disorder, depression with psychosis
Diagnostic classification system	ICD–10 (F20.x (except F20.4/F20.5), F22.x, F23.x, F24, F25.x, F28/F29,F10-F19.5, F30.2, F31.2, F31.5, F32.3/F33.3)	Not applicable	DSM-IV criteria

Note: SLaM, South London and Maudsley; CAARMS, Comprehensive Assessment of At-Risk Mental State; PLIKS, Psychosis-Like Symptoms Interview; SIPS, Structured Interview for Psychosis-risk Syndromes; ICD, International Classification of Diseases; DSM, Diagnostic and Statistical Manual of Mental Disorders.
*(a) as Fusar-Poli et al., 2017 (a) and (b) as Fusar-Poli et al., 2017 (b), ** In Orygen, those who enter the CHR clinics are followed up for two years after initial assessment with CAARMS. However, individuals entering CHR clinics at age 15 are eligible to receive care up to age 18 (Burke et al., 2022).

absence of a psychosis diagnosis in participants at the start of the follow-up (Veijola et al., 2013) (Supplement 3).

Meta-analyses

Sensitivity of the CHR approach

We pooled four sensitivity estimates from CHR studies (Burke et al., 2022; Fusar-Poli et al., 2020; Sullivan et al., 2020). The pooled estimate of the sensitivity of the CHR approach is 0.067 (95% CI: 0.015–0.150), with strong evidence for statistical heterogeneity (χ^2[3] = 157.45, p < .001; I^2 = 97.89%, τ^2 = 0.07, H^2 = 47.47) (Figure 2).

Sensitivity of the FHR approach

Blomström et al. (2016) reported two sensitivity estimates: one for 288 individuals with a paternal history of psychosis (sensitivity estimate: 0.035) and the other for 420 individuals with a maternal history of psychosis (sensitivity estimate: 0.050). We assumed that there was little overlap between individuals with a history of paternal and maternal psychotic diagnosis, as previously shown by Healy et al (2024), so we combined the two estimates to derive one single estimate (0.085) from that study (Blomström et al., 2016). We considered the lifetime FHR sensitivity estimate from Healy et al. (2024), who reported multiple estimates based on multiple time points for FHR ascertainment.

Therefore, we pooled four sensitivity estimates from all four FHR studies (Blomström et al., 2016; Debost et al., 2019; Healy et al., 2024; Veijola et al., 2013). The pooled estimate of the sensitivity of the FHR approach is 0.065 (95% CI: 0.044–0.089), with strong evidence for statistical heterogeneity (χ^2[3] = 127.16, p < .001; I^2 = 97.16%, τ^2 = 0.01, H^2 = 35.17) (Figure 3).

Sub-group analysis

Sensitivity of the CHR approach based on studies involving CHR services

We also carried out a meta-analysis of studies on "real-world" CHR clinics; that is, studies involving actual CHR services (Burke et al., 2022; Fusar-Poli et al., 2017) (as opposed to the study that actively recruited participants from the general population and applied CHR criteria (Sullivan et al., 2020)). The pooled estimate of the sensitivity of the CHR approach based on those studies is 0.056 (95% CI: 0.007–0.146), with strong evidence for statistical heterogeneity (χ^2[2] = 154.61, p < .001; I^2 = 98.67%, τ^2 = 0.07, H^2 = 75.06) (Supplement 4).

Sensitivity of the FHR approach based on studies with a low risk of bias

We meta-analysed the FHR studies with a low risk of bias (Blomström et al., 2016; Debost et al., 2019; Healy et al., 2024). The pooled estimate from this sub-group analysis is 0.066 (95% CI: 0.044–0.092), with strong evidence for statistical heterogeneity (χ^2[2] = 126.40, p < .001; I^2 = 98.32%, τ^2 = 0.01, H^2 = 59.44) (Supplement 5).

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Table 2. Characterisitcs of familial high-risk studies

	Blomström et al. (2016)	Veijola et al. (2013)	Healy et al. (2024)	Debost et al. (2019)
Study setting	Swedish nationwide birth cohort (1978–1997)	Finnish birth cohort from Oulu and Lapland provinces (1985–1986)	Finnish nationwide birth cohort (1987–1992)	Danish nationwide birth cohort (1981–1998)
Total sample (n)	1,971,623	295	368,937	882,813
FHR assessment				
Period when assessed	1991–2011	1985–2005	1987–2016	1981–2013
Age of offspring (years)	13–33	0–20	0–30	0–15
FHR defined as	History of parental psychotic diagnoses	History of parental psychotic diagnoses	History of parental psychotic diagnoses	History of parental psychotic diagnoses
Nature of parental psychosis diagnosis	Non-affective psychotic diagnoses extracted from inpatient/outpatient records	Any psychotic diagnoses extracted from inpatient records	Non-affective psychotic diagnoses extracted from inpatient records	Non-affective psychotic diagnoses extracted from inpatient/ outpatient or emergency-visit records
Parental psychosis diagnostic codes	ICD–10 (F20-F29)	ICD–8, ICD–9 (295–299), ICD–10 (F20-F33 – excluding non-psychotic mood disorders)	ICD–8 (295,297,298.10–299.99),ICD–9 (297–298),ICD–10 (F20-F29)	ICD–8 (295,297, 298.39, 301.83), ICD–10 (F20-F29)
Psychosis diagnosis among offspring				
Period when assessed	1991–2011	2007–2010	1987–2016	1996–2013
Age (years)	13–33	20.7–25.3	25–30	15–33
Nature of diagnosis	Non-affective psychotic diagnoses extracted from inpatient/outpatient records	Any psychotic diagnoses using SIPS-psychosis criteria	Non-affective psychotic diagnoses extracted from inpatient/outpatient records	Schizophrenia diagnoses extracted from inpatient/outpatient records
Diagnostic codes	ICD–9 (295, 297, and 298 except 298A and B), ICD–10 (F20–29)	Not applicable (since diagnoses made using SIPS-psychosis criteria)	ICD–10 (F20–29)	ICD–10 (F20.x.)

Note: ICD, International classification of diseases; SIPS, Structured Interview for Psychosis-risk Syndromes; FHR, familial high-risk

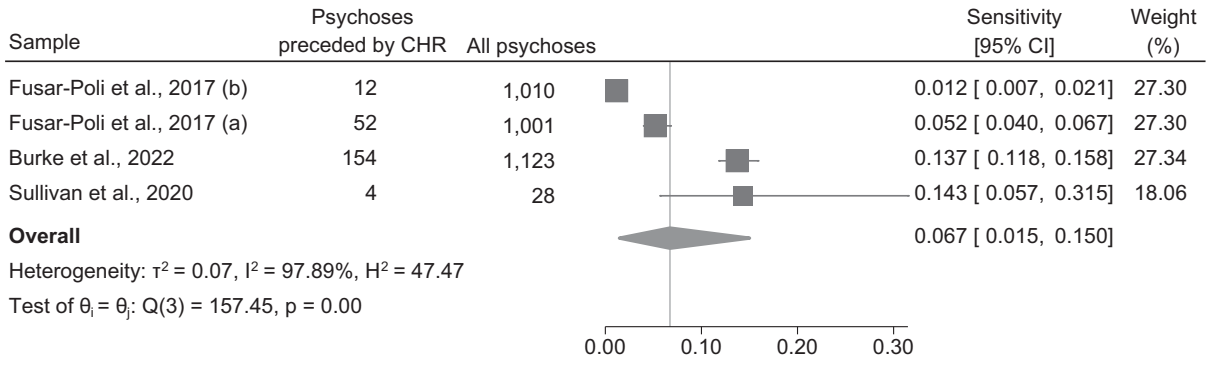

Figure 2. Pooled estimate of sensitivity of the clinical high-risk approach.
Note: Random Effects Sidik–Jonkman Model; θ: true sensitivity parameter; CHR = Clinical high-risk.

Discussion

We carried out a systematic review and meta-analysis of studies providing data on the sensitivity of CHR and FHR approaches; that is, of all future psychotic disorders in the population, what proportion do these approaches identify. We identified four CHR samples and four FHR samples reporting relevant data. The pooled point estimate for the sensitivity of the CHR approach was 6.7%. The pooled point estimate for the sensitivity of the FHR approach was 6.5%.

In terms of the CHR paradigm, three of the four included samples involved "real world" CHR services (Burke et al., 2022; Fusar-Poli et al., 2017). The pooled estimate of the sensitivity of the CHR approach from those three samples was 5.6%. The fourth CHR sample (Sullivan et al., 2020) applied CHR criteria to a general population sample (i.e., not in the context of a CHR clinic). In that study, they assessed the general population sample for psychotic symptoms at age 18 and followed them until age 24. This approach still missed a large majority (approx. 86%) of future psychotic

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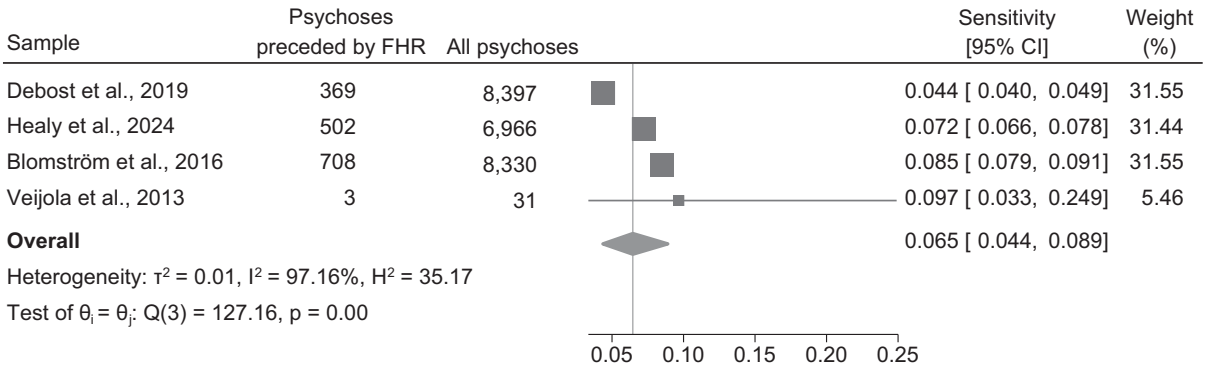

Figure 3. Pooled estimate of sensitivity of the familial high-risk approach
Note: Random Effects Sidik–Jonkman Model; θ: true sensitivity parameter; FHR = Familial high-risk.

disorder diagnoses, demonstrating the limitations of symptom-based approaches even when applied at scale.

In the case of the FHR approach, three of the four studies included total population data and, therefore, likely reflect the true sensitivity of the FHR approach in the population. As with the CHR approach, the FHR approach captured only a small minority of future psychotic disorders. Recent FHR research has also investigated parental mental health service use more broadly (not limited to parental psychotic disorders) to see if this might capture a larger proportion of future psychosis cases in offspring. Specifically, Healy et al. (2024) found that, while 7.2% of all psychotic disorders occurred in the offspring of parents with a history of psychosis, 28.7% of all psychotic disorders occurred in the offspring of parents who had a history of inpatient psychiatric admission (for any reason, not limited to psychosis) (Healy et al., 2024). This highlights opportunities to expand risk detection beyond existing approaches.

Additional approaches to identifying risk for psychosis have included following young people who have presented to the emergency department with self-harm (Bolhuis et al., 2024, 2021) and who have attended child and adolescent mental health services (Lång et al., 2022). In particular, longitudinal research in Finland (Lång et al., 2022) showed that up to half of all psychotic disorder diagnoses emerged in individuals who had, at some stage in childhood (age < 18), attended child and adolescent psychiatry services. Given international variation in the architecture and functioning of child mental health services (Signorini et al., 2017), this finding requires replication outside of Finland but suggests that child psychiatry services represent a promising avenue for future psychosis risk research.

FHR studies varied in the age of the offspring at which FHR status was determined. The study with the lowest sensitivity estimate (4.4%) had determined the FHR status up to age 15 years (Debost et al., 2019), compared to Veijola et al. (2013) up to age 20 years (sensitivity estimate: 9.7%), Healy et al. (2024) up to age 30 years (sensitivity estimate: 7.2%), and Blomström et al. (2016) between 13 and 33 years (sensitivity estimate: 8.5%). Healy et al. (2024) has found that the sensitivity of the FHR approach increases as the age of the offspring at which FHR status is determined increases, highlighting the dynamic nature of this approach. It is, however, important to point out that this study was the only population-based study that specifically aimed to calculate FHR sensitivity. The other population-based FHR studies in our review just reported incidental data that made it possible for us to also calculate FHR sensitivity but without the same fine-grained detail on age cut-offs provided by Healy et al. (2024). There was also variation in terms of the risk of bias; however, a sub-group analysis excluding the one FHR study with a high risk of bias (Veijola et al., 2013) produced a similar estimate (6%) to the main analysis (Supplement 4).

Three of the four CHR samples reported data from "real world" CHR clinics (Burke et al., 2022; Fusar-Poli et al., 2017) but the sensitivity estimates varied across the study settings: 5.2% in Lambeth and Southwark boroughs of South London (Fusar-Poli et al., 2017), 1.2% in Lewisham and Croydon boroughs of South London (Fusar-Poli et al., 2017), and 13.7% in Melbourne (Burke et al., 2022). The difference in these estimates may reflect differences in the catchment population of the clinics, outreach activity, referral systems and waiting times for CHR assessment, and the amount of immigration to and emigration from the catchment areas. For instance, London has a very dynamic migration pattern, with the South London boroughs experiencing a net positive external migration according to the 2021 census (LandTech, 2024). Such a dynamic migration pattern could affect access to services for psychosis due to the lack of a stable healthcare registration, as well as issues specific to immigrant populations, such as cultural stigma, lack of awareness, or language barriers (Pollard & Howard, 2021) – all of which could affect the sensitivity of CHR clinics in identifying individuals at risk of psychosis in these areas.

Disparities in access to mental health services mean that groups such as migrants, minoritised ethnic groups, and people living in socially deprived areas may also be less likely to come into contact with CHR clinics (Ajnakina, David, & Murray, 2019; Ajnakina et al., 2017; Morgan et al., 2006; Steele, Dewa, & Lee, 2007). We found, however, that the sensitivity estimate derived from the study by Sullivan et al. (2020) (14.3%), which screened a general population sample with CHR criteria (Sullivan et al., 2020), was in line with the estimate from the help-seeking sample from the Melbourne PACE clinic (13.7%) (Burke et al., 2022). This suggests that even if there were no barriers to accessing CHR services, the approach would still not capture a large majority of future psychosis cases.

Strengths and limitations

This review includes studies based on both help-seeking populations and general population-wide registries captured in four major bibliographic databases since their inception. All studies retrieved were conducted either in Northern European countries or Australia,

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which may limit the generalisability of our results. Further, we did not formally search for grey literature, which may have led to the exclusion of unpublished articles. One CHR study (Fusar-Poli et al., 2017) did not follow up individuals who were rated as CHR negative. This means that the sensitivity estimate for this study should be considered optimistic as it assumes that there were no false negatives (i.e., individuals who went on to develop psychosis) in the CHR negative group. Based on studies that have followed CHR negative individuals over time, this is, however, unlikely (Conrad et al., 2017). The higher the number of false negatives, the lower the true sensitivity would be for that study. We did not include approaches to assessing symptomatic risk other than those using CAARMS or SIPS criteria, such as the basic symptom (BS) approach, as other criteria are not widely used internationally in CHR services (Andreou, Bailey, & Borgwardt, 2019; Thompson, Marwaha, & Broome, 2016).

One FHR study (Blomström et al., 2016) did not report data on the overlap between offspring with maternal and paternal histories of psychosis, meaning that our combined sensitivity estimate for that study may have been overestimated, as anyone with two parents with psychosis would be counted twice in the numerator. However, Healy et al. (2024) found that only 0.3% of individuals with a psychosis diagnosis had both maternal and paternal histories of psychosis (Healy et al., 2024), meaning, it is unlikely that the true sensitivity was substantially overestimated for that individual study (Blomström et al., 2016).

Conclusions

CHR and FHR approaches have created an important clinical and research focus on psychosis prediction and prevention. The findings of this review show, however, that these strategies identify only a small minority of all individuals who will go on to develop psychotic disorders in the population – just 6–7%, each. These findings highlight the need for additional approaches to psychosis risk detection if we wish to increase the capacity for psychosis prediction and, ultimately, prevention, rather than relying on any single approach.

Supplementary material. The supplementary material for this article can be found at http://doi.org/10.1017/S0033291724003520.

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Authors contribution. AT, IKG, and IK conceptualised the review design. AT and IKG drafted the review protocol, with feedback from IK and KOH. IK and KOH supervised the review process. AT and IKG performed data analyses. AT, IKG, and IK wrote the manuscript draft, with critical feedback from KOH, CH, MJ, VK and UL.

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