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REVIEW ARTICLE

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# Guidelines for the prevention of psychosis from the World Federation of Societies of Biological Psychiatry (WFSBP) and EPI Canada

Marco Solmi[a,b,c,d†], Christoph U. Correll[d,e,f†], Tommaso Boldrini[g,h†], Jean M. Addington[i], Edgar Barbezat[c*], Stella Bassetto[j,k], Andreas Bechdolf[l,m,n], Dan Devoe[o], Joseph Firth[p,q], Paolo Fusar-Poli[r,s,t], Ary Gadelha[u], Renan Göksal[v], Matcheri Keshavan[w], Eoin Killackey[x,y], Nikolaos Koutsouleris[z,aa,ab], Gabriele Lo Buglio[a,c], Mirko Manchia[ac,ad,ae], Patrick McGorry[x,y], Jai Shah[af,ag], Helen J. Stain[ah], Philip G. Tibbo[ai,aj,ak], Thomas Hastings[al,am], Howard C. Margolese[ag,an], Nicola Otter[ao], Eduard Vieta[ap], Liang-Jen Wang[aq], Scott W. Woods[ar], Lakshmi N. Yatham[as], Alison R. Yung[at,au], Muhammad Omair Husain[av,aw], Peter Falkai[ax,ay,az], Michael Berk[at] and Andre F. Carvalho[at]

[a]SCIENCES lab, Department of Psychiatry, Faculty of Medicine, University of Ottawa, Ontario, Canada; [b]Department of Mental Health, The Ottawa Hospital, Ontario, Canada; [c]Ottawa Hospital Research Institute (OHRI), Ottawa; [d]Department of Child and Adolescent Psychiatry, Charité Universitätsmedizin, Berlin, Germany; [e]Department of Psychiatry, Zucker Hillside Hospital, Northwell Health, Glen Oaks, USA; [f]Department of Psychiatry and Molecular Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, USA; [g]Department of Psychology and health sciences, Pegaso Telematic University, Naples, Italy; [h]Department of Psychiatry, Faculty of Medicine, University of Ottawa, Ontario, Canada; [i]Department of Psychiatry, Hotchkiss Brain Institute, University of Calgary, Calgary, Canada; [j]Social and Cognitive Neuroscience Lab (ScnLab), Mackenzie Presbyterian University, Brazil; [k]Institute of Psychiatry, University of São Paulo, Brazil; [l]Department of Psychiatry, Psychotherapy, and Psychosomatics incorporating FRITZ am Urban and soulspace, Vivantes Hospital am Urban and Vivantes Hospital im Friedrichshain, Berlin, Germany; [m]Department of Psychiatry and Psychotherapy, CCM, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin; [n]German Center for Mental Health (DZPG), Berlin-Potsdam site, Germany; [o]Department of Psychology, Mount Royal University; [p]Division of Psychology and Mental Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK; [q]NICM Health Research Institute, Western Sydney University, Westmead, Australia; [r]Department of Brain and Behavioral Sciences, University of Pavia, Italy; [s]Early Psychosis: Interventions and Clinical-detection (EPIC) Lab, Department of Psychosis Studies, King's College London, UK; [t]Outreach and Support in South-London (OASIS) service, South London and Maudsley (SLaM) NHS Foundation Trust, UK; [u]Schizophrenia Program (PROESQ), Department of Psychiatry and Psychological Medicine, Escola Paulista de Medicina, Universidade Federal de São Paulo (EPM/UNIFESP), São Paulo-SP, Brazil; [v]Department of Developmental Psychology and Socialization, University of Padova, Padova, Italy; [w]Department of Psychiatry, Harvard Medical School Department of Psychiatry at Beth Israel Deaconess Medical Center and Massachusetts Mental Health Center, Boston, USA; [x]Orygen, The National Centre of Excellence in Youth Mental Health, Parkville, Australia; [y]The University of Melbourne, Melbourne, Australia; [z]Max Planck Institute for Psychiatry, Ludwig-Maximilian-University, Munich, Germany; [aa]Department of Psychiatry and Psychotherapy, Ludwig-Maximilian-University, Munich, Germany; [ab]Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom; [ac]Unit of Psychiatry, Department of Medical Sciences and Public Health, University of Cagliari; [ad]Unit of Clinical Psychiatry, Department of Medical Specialties, University Hospital Agency of Cagliari; [ae]Department of Pharmacology, Dalhousie University, Halifax, Canada; [af]Douglas Research Centre, Montreal, Canada; [ag]Department of Psychiatry, McGill University, Montreal, Canada; [ah]Professor of Psychology, TIPS Centre for Clinical Research in Psychosis, Stavanger, Norway; [ai]Department of Psychology and Neuroscience, Dalhousie University, Halifax, Canada; [aj]Department of Psychiatry, Dalhousie University, Halifax, Canada; [ak]Nova Scotia Health Authority, Halifax, Canada; [al]Department of Psychiatry, McMaster University, Hamilton, Canada; [am]Department of Psychiatry, University of Toronto, Toronto, Canada; [an]McGill University Health Centre, Montreal, Canada; [ao]EPI Canada, Canada; [ap]Bipolar and Depressive Disorders Unit, Hospital Clinic, Institute of Neuroscience, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Spain; [aq]Department of Child and Adolescent Psychiatry, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung city, Taiwan; [ar]Department of Psychiatry, Yale University New Haven Connecticut, USA; [as]Mood Disorders Centre, University of British Columbia, Vancouver, Canada; [at]Institute for Mental and Physical Health and Clinical Translation (IMPACT), Deakin University and Barwon Health, Australia; [au]School of Health Sciences, University of Manchester, UK; [av]Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, Canada; [aw]Department of Psychiatry, Temerty Faculty of Medicine, University of Toronto, Toronto, Canada; [ax]Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich, Germany; [ay]Max Planck Institute of Psychiatry, Munich, Germany; [az]German Center for Mental Health (DZPG), Partner site Munich/Augsburg, Augsburg, Germany

**CONTACT** Marco Solmi msolmi@toh.ca SCIENCES lab, Department of Psychiatry, Faculty of Medicine, University of Ottawa, Ontario, Canada
†These authors have contributed equally to this work and share first authorship
*lived experience board member of the hatching ideas lab
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**ABSTRACT**

**Objective:** To prepare evidence-based guidelines on psychosis prevention.

**Methods:** We reviewed evidence on risk factors for/age at onset of psychosis, tools to assess clinical high-risk of psychosis (CHR-P), transition rates, risk calculation/ethical considerations around risk communication, CHR-P biological/clinical correlates, efficacy/cost-effectiveness of interventions/psychosis prevention services. The World Federation of Societies of Biological Psychiatry framework was used to grade evidence regarding interventions/services, elaborating guidelines with evidence-/consensus-based clinical recommendations to prevent psychosis in CHR-P subjects.

**Results:** At the service organisation level, (i) psychosis indicated prevention services might be implemented in close collaboration with early intervention services for psychosis to minimise duration of untreated illness, (ii) intake age criteria should be between 14 to 35, (iii) services should allow access to persons with cannabis use disorder. At the assessment and risk communication level, in clinical settings: (iv) staff in mental health services should be trained in administering/rating CHR-P assessment tools, (v) administer them, (vi) be trained in using/interpreting risk calculators, and (vii) in communicating risk, (viii) only use validated risk calculators, keeping a human-to-human interaction. Also, (ix) prevention services should assess comorbid mental disorders. At the intervention level: (x) staff should offer treatment for abstinence from cannabis, (xi) offer evidence-based treatment for comorbid mental disorders, and (xii) offer treatment for CHR-P based on patient preference, following the 'first do no harm' principle.

**Conclusions:** Prevention services should be implemented, including interventions for cannabis use, reducing the duration of untreated psychosis, and treating comorbid mental disorders.

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Clinical guidelines; psychosis; prevention; clinical high risk for psychosis; schizophrenia

## 1. Background

Psychotic disorders, such as schizophrenia, are associated with considerable burden (Solmi, Seitidis, et al. 2023) and reduced life expectancy compared with the general population (Correll et al. 2022) due to suicide, but most frequently as a result of co-occurring physical conditions (Stubbs et al. 2016; Correll et al. 2017). The reduced life expectancy in people with schizophrenia is aggravated by the low quality of physical healthcare that people with schizophrenia receive (Solmi, Firth, et al. 2020; Solmi, Fiedorowicz, et al. 2021). In the absence of early interventions, schizophrenia often has a chronic course, severely impacting patients' functioning and their families' environment (Kahn et al. 2015). Effective treatments for schizophrenia are available, with antipsychotics being the cornerstone of treatment at all stages of the disease (Solmi et al. 2017; Correll, Rubio, et al. 2018; McCutcheon et al. 2025). Well-evidenced psychosocial interventions should augment pharmacological treatment, in particular within early intervention services (Correll, Galling, et al. 2018). These include family interventions (for the early stages of schizophrenia), as well as cognitive behavioural therapy (CBT), cognitive remediation therapy, and individual placement and support (Solmi, Croatto, et al. 2023). While considered a new treatment modality, brain stimulation is also effective for schizophrenia, yet they are not first-line treatments (Rosson et al. 2022). Lifestyle interventions are increasingly becoming accepted and recommended (Gurusamy et al. 2018; Stubbs et al. 2018; Firth et al. 2020). Despite the several treatment options, none of these are disease-modifying. Hence, interventions that prevent or delay the onset of schizophrenia are needed, especially considering that the duration of untreated psychosis has been associated with poorer medium and long-term outcomes (Howes et al. 2021).

While prevention has been largely implemented in other branches of medicine, it is only recently being applied to mental health care (Arango et al. 2018; Kotlicka-Antczak et al. 2020; Fusar-Poli, Correll, et al. 2021; Estradé et al. 2022). Within mental health, many studies have focused on the indicated prevention of psychosis, mainly in subjects presenting psychotic symptoms that do not meet the intensity or duration criteria for a Diagnostic and Statistical Manual of Mental Disorders (DSM)- or International Classification of Diseases (ICD)- defined psychotic disorder. The presence of subthreshold psychotic symptoms has been defined as an ultra-high or clinical high-risk (UHR/CHR) state, and has been introduced more than 25 years ago in Melbourne, Australia (Yung et al. 2005). Currently, evidence on the possibility of preventing psychosis with specific interventions has been conflicting (Mei et al. 2021; Fusar-Poli, Radua, et al. 2022), and has mainly focused on subjects meeting criteria for CHR of psychosis (CHR-P), who comprise the majority of those ultimately developing a psychotic disorder (Shah et al. 2017; Benrimoh et al. 2024).

The following guidelines provide a comprehensive overview on risk factors for psychosis, the definition and tools to assess CHR-P status, its biological

correlates and comorbid mental disorders, the literature around risk of transition from CHR-P to psychosis and around additional outcomes in CHR-P. We also reviewed literature around individual randomised controlled trials (RCTs) testing interventions to prevent psychosis, (network) meta-analyses pooling results of these RCTs, and finally observational or simulation studies reporting on the clinical and cost-effectiveness outcomes of psychosis prevention services. Recommendations for the indicated prevention of psychosis in subjects meeting CHR-P criteria were made, based on consensus, on the evaluation of RCTs and evidence regarding psychosis prevention services according to the World Federation of Societies of Biological Psychiatry (WFSBP) guidance for preparing clinical guidelines (Hasan et al. 2019).

## 2. Methods

We summarised available evidence adopting several strategies including meta-umbrella, umbrella, systematic reviews, or relying on previous systematic evidence synthesis recently completed, on a set of a-priori selected clinically relevant areas related to prevention of psychosis. Starting from the literature knowledge of authors, we identified relevant reviews, and updated the search to 19/09/2024 if the most updated evidence synthesis publication was published before September 2022 (more than two years old), prioritising meta-umbrella over umbrella and systematic reviews, and following the same methodology of the most updated review (e.g. an updated umbrella review for (meta-) umbrella reviews, an updated systematic review for systematic reviews). We chose September 2022, i.e. two years, for feasibility considerations given the breadth of this evidence synthesis. Where no previous evidence synthesis was available, we conducted one, with three exceptions. First, we did not update reviews that included over 100 epidemiologic studies, since we anticipated that adding few studies would have not been likely to materially change results. Second, we did not conduct systematic reviews to identify the most frequently used psychometric tools to assess CHR-P, given the robust expertise of the authors on this subject (i.e. the tools are already known). Third, we did not conduct a systematic review for ethical considerations around the risk in assessing and communicating risk in psychosis prediction, since the subject would not easily lend itself to quantitative evidence syntheses. Instead, we leveraged the report of a recent workshop completed by experts in the area, well representing the multifaceted set of considerations around ethics and risk prediction. We then graded evidence following the WFSBP guidelines for clinical guidelines development (Hasan et al. 2019).

The a-priori list of topics, search keys, study selection flows, as well as methodological framework used for guideline preparation are detailed in the supplementary material, and in Table 1. The approach followed to review literature on each specific area is summarised below, including the criteria grading credibility of the evidence on risk factors (Table 2). Finally, each recommendation reached a consensus among co-authors as detailed below.

**Table 1.** World Federation of Societies of Biological Psychiatry grading system, and grades of recommendations.

Grades of recommendation are based on a synthesis of: i. Level of evidence (see Table 10), and ii. Acceptability (criteria for grading adapted and modified from (AWMF 2012; GRADE 2017), rated 'strong', 'limited', and 'weak'. Acceptability criteria are factors considered are risk-benefit ratio (e.g. adverse effects, interactions), cost-benefit ratio, applicability in the target population, ethical and legal aspects, preferences of service users, practicability.

The algorithm of evaluating the acceptability to develop GoRs from LoEs is detailed below, for positive and negative recommendations.

| Recommendations for using the intervention | | | Recommendations for using the intervention | | |
|---|---|---|---|---|---|
| Strong | 1 | 'A' LoE and GOOD acceptability | Strong | **1** | Strong negative evidence (LoE -A) |
| Limited | 2 | 'A' LoE and MODERATE acceptability OR 'B' LoE and GOOD acceptability | Limited | **2** | Limited negative evidence (LoE -B) |
| **Weak** | **3** | 'A' LoE and POOR acceptability OR 'B' LoE and MODERATE/POOR acceptability OR 'C' LoE and GOOD/MODERATE/ | **Weak** | **3** | Weak negative evidence (LoE-C) |
| **No recommendation possible** | **4** | Insufficient evidence (LoE D) to give recommendations | **No recommendation possible** | **4** | Insufficient evidence (LoE D) to give recommendations |

*Legend.* GoR: grade of recommendation; LoE: level of evidence.

**Table 2.** Risk factors and biomarkers with significant association with psychosis reported in meta-analyses and umbrella reviews, and their credibility according to established criteria (Ioannidis 2009; Fusar-Poli and Radua 2018; Solmi, Dragioti, Croatto, Radua, Borgwardt, Carvalho, Demurtas, Mosina, Kurotschka, Shin, et al. 2021; Solmi, De Toffol, et al. 2023).

| Risk factor | k | Association odds ratio | Credibility |
|---|---|---|---|
| Individual medical, psychiatric, psychological factors | | | |
| Ultra-high-risk state for psychosis | 9 | 9.32 (4.91–17.32) | Convincing |
| Cannabis use | 18 | 1.71 (1.47–2.00) | Highly suggestive/Convincing |
| Poor olfactory identification ability | 55 | 5.26 (NA-NA) | Highly suggestive |
| Trait anhedonia | 44 | 4.41 (NA-NA) | Highly suggestive |
| Low premorbid IQ | 16 | 2.13 (NA-NA) | Highly suggestive |
| Childhood social withdrawal | 15 | 2.91 (NA-NA) | Suggestive |
| Tobacco use | 17 | 2.34 (1.65–3.33) | Suggestive |
| Non-right handedness | 41 | 1.58 (1.35–1.86) | Suggestive |
| Neurological soft signs | 8 | 27.59 (NA-NA) | Weak |
| Poor olfactory memory ability | 2 | 20 (NA-NA) | Weak |
| Neuroticism | 8 | 8.76 (NA-NA) | Weak |
| Epilepsy | 4 | 7.84 (2.87–21.40) | Weak |
| Harm avoidance | 7 | 5.92 (NA-NA) | Weak |
| Poor self-directedness | 7 | 5.88 (NA-NA) | Weak |
| Heavy cannabis use | 2 | 5.17 (3.64–7.36) | Weak |
| Poor olfactory discrimination ability | 8 | 5.00 (NA-NA) | Weak |
| Poor extraversion | 8 | 5.00 (NA-NA) | Weak |
| Poor olfactory hedonic ability | 10 | 4.00 (NA-NA) | Weak |
| Psychotic-like experiences | 4 | 3.84 (2.55–5.79) | Weak |
| Poor conscientiousness | 7 | 3.45 (NA-NA) | Weak |
| Hearing impairment | 3 | 3.15 (1.25–7.95) | Weak |
| Poor olfactory detection ability | 18 | 3.12 (NA-NA) | Weak |
| High Self-transcendence | 7 | 3.03 (NA-NA) | Weak |
| Poor motor function pre-onset of psychosis | 4 | 2.78 (NA-NA) | Weak |
| Antisocial and externalising behaviour | 3 | 2.39 (NA-NA) | Weak |
| Poor agreeableness | 6 | 2.38 (NA-NA) | Weak |
| Delay in walking unsupported | 5 | 2.37 (NA-NA) | Weak |
| Poor cooperativeness | 7 | 2.33 (NA-NA) | Weak |
| Hypoalgesia | 9 | 2.31 (NA-NA) | Weak |
| Poor reward dependence | 7 | 2.17 (NA-NA) | Weak |
| Poor openness | 7 | 2.04 (NA-NA) | Weak |
| Delay in standing unsupported | 4 | 1.58 (NA-NA) | Weak |
| Poor persistence (trait of temperament) | 7 | 1.54 (NA-NA) | Weak |
| Traumatic brain injury | 8 | 1.49 (1.09–2.05) | Weak |
| Delay in sitting unsupported | 4 | 1.41 (NA-NA) | Weak |
| Total A-B ridge count | 13 | 1.32 (NA-NA) | Weak |
| Delay in holding head up | 3 | 1.26 (NA-NA) | Weak |
| *Biomarkers* | | | |
| High Serum C-reactive protein | 15 | 2.96 (1.75–5.01) | Suggestive |
| Low serum brain-derived neurotrophic factor | 17 | 2.94 (1.61–5.55) | Suggestive |
| High Serum interleukin 6 | 29 | 2.61 (1.55–4.40) | Suggestive |
| High Plasma MDA | 4 | 42.88 (3.15–583.91) | Weak |
| Low plasma TAS | 3 | 16.67 (6.25–50.00) | Weak |
| High Serum IL-8 | 4 | 10.57 (1.81–61.82) | Weak |
| High Serum malondialdehyde | 17 | 9.60 (3.27–28.19) | Weak |
| Low serum 25(OH)D | 6 | 8.33 (2.78–25.00) | Weak |
| Low serum NGF | 8 | 7.14 (1.18–50.00) | Weak |
| High Serum DPA | 14 | 7.10 (3.42–14.75) | Weak |
| High Serum S100B | 19 | 5.81 (3.03–11.17) | Weak |
| High Serum IL-1β | 11 | 5.45 (2.09–14.19) | Weak |
| Impaired glucose tolerance | 7 | 4.55 (2.10–9.84) | Weak |
| Low serum Zink | 9 | 4.35 (1.33–14.29) | Weak |
| High Serum prolactin | 12 | 4.26 (1.92–9.45) | Weak |
| High Serum sIL-2R | 9 | 3.55 (2.00–6.32) | Weak |
| High Serum LA | 16 | 3.45 (1.67–7.13) | Weak |
| High Plasma TBARS | 12 | 3.20 (1.51–6.78) | Weak |
| High Serum glutamate | 10 | 3.17 (1.46–6.90) | Weak |
| High Serum AA | 19 | 3.16 (1.84–5.43) | Weak |
| High Serum TNF-α | 24 | 2.80 (1.50–5.21) | Weak |
| Low Serum ADH | 11 | 2.78 (1.30—5.88) | Weak |
| High Serum DHA | 18 | 2.52 (1.19–5.35) | Weak |
| High Serum IL-1RA | 4 | 2.46 (1.07–5.63) | Weak |
| High Serum TGF-β | 6 | 2.23 (1.29–3.84) | Weak |
| Low plasma uric acid | 4 | 1.89 (1.13–3.12) | Weak |
| Serum homocysteine (Per 5 mmol/l increase) | 8 | 1.68 (1.25–2.25) | Weak |
| Insulin resistance | 8 | 1.68 (1.09–2.59) | Weak |
| High Serum serine | 19 | 1.66 (1.04–2.66) | Weak |
| High Serum leptin | 28 | 1.62 (1.14–2.30) | Weak |
| High Serum morning cortisol | 42 | 1.60 (1.16–2.21) | Weak |

(*Continued*)

**Table 2.** Continued.

| Risk factor | k | Association odds ratio | Credibility |
|---|---|---|---|
| Unsaturated fatty acids supplementation | 9 | 0.59 (0.39–0.89) | Weak |
| *Pregnancy factors* | | | |
| Famine | 3 | 1.61 (1.51–1.71) | Convincing |
| Any famine or nutritional deficiency | 13 | 1.40 (1.17–1.68) | Suggestive |
| Herpes simplex type 2 infection | 5 | 1.35 (1.16–1.58) | Suggestive |
| Diabetes in pregnancy | 2 | 10.12 (1.84–55.72) | Weak |
| Polyhydramnios | 3 | 3.05 (1.15–8.06) | Weak |
| Maternal stress | 4 | 2.40 (1.15–5.01) | Weak |
| Premature ruptured membranes | 4 | 2.29 (1.38–3.80) | Weak |
| Threatened premature delivery | 2 | 2.05 (1.02–4.10) | Weak |
| Pre-pregnancy and pregnancy maternal obesity | 4 | 1.99 (1.26–3.14) | Weak |
| Uterine atony | 3 | 1.93 (1.35–2.76) | Weak |
| Suboptimal number of antenatal care visits | 4 | 1.83 (1.42–2.36) | Weak |
| Antepartum haemorrhage | 14 | 1.63 (1.12–2.38) | Weak |
| Foetal hypoxia | 6 | 1.63 (1.11–2.40) | Weak |
| Maternal hypertension | 7 | 1.40 (1.10–1.78) | Weak |
| Toxoplasma infection | 4 | 1.30 (1.04–1.62) | Weak |
| Unspecified maternal infection | 9 | 1.27 (1.06–1.53) | Weak |
| *Maternal and paternal factors* | | | |
| Maternal psychosis | 6 | 7.61 (6.29–9.21) | Highly suggestive |
| Any maternal psychopathology | 9 | 4.60 (2.74–7.73) | Highly suggestive |
| Any paternal psychopathology | 5 | 2.73 (2.33–3.19) | Highly suggestive |
| Three or more previous pregnancies | 10 | 1.30 (1.16–1.45) | Suggestive |
| Maternal age < 20 years old | 22 | 1.17 (1.07–1.27) | Suggestive |
| Parental severe mental illness | 9 | 5.94 (2.99–11.79) | Weak |
| Parental communication deviance | 19 | 5.80 (3.99–8.44) | Weak |
| Paternal age > 45 years | 4 | 2.36 (1.35–4.11) | Weak |
| Maternal affective disorder | 3 | 2.26 (1.09–4.70) | Weak |
| Low paternal socio-economic status | 9 | 1.30 (1.02–1.65) | Weak |
| Paternal age > 34 years old | 13 | 1.28 (1.06–1.55) | Weak |
| Maternal age 30–34 years old | 20 | 1.05 (1.01–1.09) | Weak |
| *Ethnicity or migration-related factors* | | | |
| Black-Caribbean ethnicity in England | 9 | 4.87 (3.96–6.00) | Convincing |
| Ethnic minority in low ethnic density area | 5 | 3.71 (2.47–5.58) | Highly suggestive |
| Second-generation immigrant | 26 | 1.68 (1.42–1.92) | Highly suggestive |
| North-African immigrants in Europe | 12 | 2.22 (1.58–3.12) | Suggestive |
| Ethnic minority in high ethnic density area | 5 | 2.11 (1.39–3.20) | Suggestive |
| First-generation immigrant | 42 | 2.10 (1.72–2.56) | Suggestive |
| Black African ethnicity in England | 4 | 4.72 (3.30–6.77) | Weak |
| Asian ethnicity in England | 6 | 2.83 (1.59–5.05) | Weak |
| Other white ethnicity in England | 3 | 2.62 (1.35–5.10) | Weak |
| Mixed ethnicity in England | 3 | 2.19 (1.08–4.44) | Weak |
| *Foetal growth and gestational age* | | | |
| Birth weight < 2 kg | 14 | 1.84 (1.53–2.22) | Convincing |
| Birth weight < 2.5 kg | 25 | 1.53 (1.31–1.78) | Convincing |
| Small for gestational age | 12 | 1.40 (1.25–1.57) | Convincing |
| Birth weight 2.5–2.999 kg | 17 | 1.23 (1.15–1.31) | Convincing |
| Minor physical anomalies | 14 | 5.30 (NA-NA) | Highly suggestive |
| Congenital malformation | 10 | 2.31 (1.29–4.13) | Weak |
| Small head circumference | 2 | 1.41 (1.00–1.97) | Weak |
| Premature birth | 24 | 1.35 (1.12–1.62) | Weak |
| Birth length < 49 cm | 8 | 1.17 (1.05–1.32) | Weak |
| *Labour season, labour complications, and delivery complications* | | | |
| Unspecific obstetric complications | 21 | 1.52 (1.19–1.94) | Weak |
| Winter (Nordic countries) | 11 | 1.05 (1.03–1.08) | Suggestive |
| Winter to spring (Nordic countries) | 27 | 1.04 (1.02–1.06) | Suggestive |
| Incubator or resuscitation | 8 | 2.12 (1.29–3.47) | Weak |
| Asphyxia state | 9 | 1.93 (1.30–2.88) | Weak |
| Definite obstetric complication* | 9 | 1.83 (1.21–2.77) | Weak |
| *Individual infections* | | | |
| Toxoplasma IgG | 42 | 1.82 (1.51–2.18) | Suggestive |
| Chlamydia psittaci | 2 | 29.05 (8.91–94.96) | Weak |
| Human endogenous retrovirus type W | 5 | 19.78 (6.50–60.22) | Weak |
| Chlamydia pneumoniae | 3 | 6.02 (2.86–12.66) | Weak |
| Herpes simplex type 2 infection | 6 | 1.44 (1.14–1.81) | Weak |
| Borna disease virus | 21 | 1.36 (1.09–1.70) | Weak |
| *Individual or environmental stress* | | | |
| Adult stressful events | 13 | 3.11 (2.31–4.18) | Highly suggestive |
| Childhood adversities | 34 | 2.80 (2.34–3.34) | Highly suggestive |
| Any psychological trauma | 25 | 2.66 (1.99–3.56) | Highly suggestive |
| Childhood trauma | 23 | 2.49 (1.86–3.33) | Highly suggestive |
| Urbanicity | 8 | 2.39 (1.63–3.51) | Suggestive |
| Sexual abuse | 2 | 12.24 (3.92–38.17) | Weak |

(*Continued*)

**Table 2.** Continued.

| Risk factor | k | Association odds ratio | Credibility |
|---|---|---|---|
| Adult negative life events | 6 | 5.34 (3.84–7.43) | Weak |
| Disadvantaged group | 3 | 2.27 (1.21–4.27) | Weak |
| *Risk factors for transition to psychosis within subjects at clinical high risk for psychosis* | | | |
| Attenuated positive symptoms | 49 | 2.563 (NA – NA) | Highly suggestive |
| Poor global functioning | 49 | 1.69 (NA – NA) | Highly suggestive |
| Negative symptoms | 49 | 2.68 (NA – NA) | Suggestive |
| Disorganised/cognitive symptoms | 18 | 2.48 (NA – NA) | Weak |
| General symptoms | 21 | 2.27 (NA – NA) | Weak |
| Unemployment | 7 | 1.81 (1.31–2.5) | Weak |
| Right handedness | 16 | 1.60 (1.04–2.46) | Weak |
| Stress/trauma | 11 | 1.15 (1.04–1.26) | Weak |
| Male sex | 66 | 1.18 (1.03–1.34) | Weak |
| Total symptoms | 29 | 1.74 (NA–NA) | Weak |

*Legend.* 25(OH)D, 25-Hydroxyvitamin D; AA, Arachidonic Acid; ADH, Vasopressin; DHA, Docosahexaenoic Acid; DPA, Docosapentaenoic Acid; IL-1β, Interleukin-1 Beta; IL-1RA, Interleukin-1 Receptor Antagonist; IL-8, Interleukin-8; LA, Linoleic Acid; MDA, Malondialdehyde; NGF, Nerve Growth Factor; S100B, S100 Calcium-Binding Protein B; sIL-2R, Soluble Interleukin-2 Receptor; TAS, Total Antioxidant Status; TBARS, Thiobarbituric Acid Reactive Substances; TGF-β, Transforming Growth Factor Beta; TNF-α, Tumour Necrosis Factor Alpha. When two meta-analyses reported on the same risk factor, we included the one with the largest number of studies, *, according to Lewis-Murray Obstetric Complications Scale. Edited from (Belbasis et al. 2018; Radua et al. 2018; Davies, Segre, et al. 2020; Oliver, Reilly, et al. 2020; Arango et al. 2021; Gao et al. 2022; Solmi, De Toffol, et al. 2023).

### 2.1. Risk factors for psychosis in the general population and in individuals at CHR-P

For risk factors for psychosis, we considered a meta-umbrella review published before September 2022 that systematically reviewed the literature on risk factors for mental disorders (Arango et al. 2021), and updated it, also searching for meta-analyses reporting on risk or protective factors for psychosis in any population, including also those meeting CHR-P criteria, and grading the credibility into convincing, highly suggestive, suggestive, weak, or no significant association based on quantitative criteria accounting for several types of bias, as already extensively applied in previous works (Bortolato et al. 2017; Dragioti et al. 2019; Kim et al. 2019; Solmi, Veronese, et al. 2020; Arango et al. 2021; Solmi, Civardi, et al. 2021; Solmi, Dragioti, Arango, et al. 2021; Solmi, Dragioti, Croatto, Radua, Borgwardt, Carvalho, Demurtas, Mosina, Kurotschka, Thompson, et al. 2021; Solmi, Radua, et al. 2021). The criteria to grade the credibility of the evidence are detailed in the eMethods section. Modifiable factors with convincing evidence were considered as potential outcomes in the recommendation section.

### 2.2. Definition of CHR-P, and assessment tools

We described the structure of the two most frequently used tools to measure CHR-P status, namely the Comprehensive Assessment of At-Risk Mental State (CAARMS) (Yung et al. 2005), and Structured Interview for Prodromal Symptoms (SIPS) (Miller et al. 2003), their subscales and symptom domains, the criteria of each tool for different CHR-P subgroups, and differences with the brief psychotic disorder listed in the Diagnostic and Statistical Manual of Mental Disorders 5-Text Revision (DSM-5-TR) (APA 2022). In addition, given the emerging international partnerships and ongoing harmonisation efforts in the field, we conducted a systematic review to identify articles on international statements and consortia introducing novel psychometric tools for measuring CHR-P status. The tools to assess CHR-P based on basic symptoms were also mentioned given their longstanding historical relevance and their potential role in future research. Regarding the prognostic accuracy of psychometric instruments to assess the risk of psychosis, we identified a systematic review with meta-analysis published in September 2022.

### 2.3. Biological correlates of clinical high risk of psychosis

We conducted a meta-umbrella review reporting on the biological factors associated with CHR-P status. In addition, we conducted an umbrella review of previous meta-analyses and large consortium brain imaging studies to identify overall and regional structural, functional, metabolic, and electric differences between the brain of subjects with CHR-P and healthy controls.

### 2.4. Comorbid mental disorders of clinical high risk of psychosis

A subgroup among authors of these guidelines conducted a systematic review of the prevalence of comorbid mental disorders in CHR-P that has been published after September 2022 (Solmi, Soardo, et al. 2023) and included over 100 studies. Hence, no additional evidence synthesis was conducted for this subject. For the scope of these guidelines, we report the pooled prevalence of concomitant mental disorders in

subjects meeting criteria for CHR-P status, to inform the assessment and care to be offered in services for prevention of psychosis. We also descriptively report the impact of concomitant mental disorders on functioning in CHR-P status, on transition to psychosis after meeting CHR-P criteria. Finally, we describe the course over time of the prevalence of comorbid mental disorders after meeting CHR-P criteria at baseline.

### 2.5. Age at onset of psychosis, epidemiology of transition from clinical high risk of psychosis to psychosis, psychosis prediction models, and ethical considerations in estimating and communicating risk to inform clinical implementation of psychosis prevention

Meta-epidemiological evidence on the age at onset of psychosis and transition rates from CHR-P to psychosis should inform the age threshold to access psychosis prevention services, clinical decision-making, and resource allocation. A subgroup among authors of these guidelines recently conducted large scale (i.e. more than 100 epidemiologic studies included) meta-analyses on age at onset of mental disorders (Solmi, Radua, et al. 2022), and on the risk of transition to psychosis in subjects with CHR-P status over time (Salazar de Pablo, Davies, et al. 2021; Salazar de Pablo, Radua, et al. 2021). Hence, no additional evidence synthesis was conducted for this subject. Also, we updated a systematic review reporting on prediction and prognosis models with a proper internal or external validation in mental health research (Salazar de Pablo, Studerus, et al. 2021), narrowing our focus on CHR-P status and prediction of psychosis onset. Finally, we included the published report of a previous workshop specifically focusing on ethical considerations around risk estimates and communicating risk of transition to psychosis (Fusar-Poli, Manchia, et al. 2022).

### 2.6. Randomised controlled trials to prevent psychosis

Given that umbrella reviews miss including individual RCTs that have been published after the most updated systematic reviews (Mei et al. 2021; Zheng et al. 2022), we also conducted a PRISMA 2020 (Page et al. 2021)-compliant systematic review of RCTs for prevention of psychosis. Recent RCTs might change the conclusions based on previous (network) meta-analyses. Given the rapid expansion of this research field, our systematic review also included ongoing RCTs and those without available results, highlighting evolving trends. We searched Embase, PsycInfo, MEDLINE, CINAHL, and clinical trials.gov up to September 19th, 2024. The search key is reported in eTable 1. Inclusion criteria were RCTs including subjects with CHR-P status according to explicit criteria. No restrictions were applied to the specific instrument used to define CHR-P, the type of intervention or control condition, and outcome of interest. We extracted author-defined primary and secondary outcomes. The primary outcome of this systematic review was transition to psychosis, in order to inform the guidelines for the indicated prevention of psychosis.

### 2.7. Meta-analyses and network meta-analyses of randomised controlled trials to prevent psychosis

We updated a previous umbrella review of (network) meta-analyses that included RCTs in subjects with CHR-P (Fusar-Poli, Davies, et al. 2019) conducted by a subgroup of the authors, following the PRIOR guidance (Gates et al. 2022). Inclusion criteria were systematic reviews with (network) meta-analyses of RCTs including subjects with CHR-P status according to explicit criteria. No restrictions were applied to the specific instrument used to define CHR-P, the type of intervention or control condition, and outcome of interest. We extracted author-defined primary and secondary outcomes. The primary outcome of this umbrella review was transition to psychosis, in order to inform the guidelines for the indicated prevention of psychosis.

### 2.8. Studies comparing psychosis prevention services with other services, and cost-effectiveness of psychosis prevention services

We updated a systematic review of cohort studies comparing clinical outcomes of psychosis prevention services versus other services (Sizer et al. 2022).

We conducted a PRISMA 2020 (Page et al. 2021) compliant systematic review on cost-effectiveness of psychosis prevention services. Inclusion criteria were cohort studies or simulated cohort studies focusing on cost-effectiveness of psychosis prevention services. No restrictions were applied to the specific instrument used to define CHR-P status, the type of control service, outcome of interest, and cost-effectiveness analysis. We extracted author-defined primary and secondary outcomes.

### 2.9. Clinical recommendations development

The recommendations were developed based on the available evidence and circulated to the panel for voting on a 5-point Likert scale (1 = completely disagree to 5 = completely agree). Consensus was defined as at least 80% of panel members rating 4 or 5. Feedback on the whole guidelines was also collected *via* email. Recommendations not reaching consensus were planned to be revised and resubmitted for voting until consensus was achieved.

## 3. Results

### 3.1. Literature review

#### 3.1.1. Risk factors for psychosis in the general population and in individuals at CHR-P

Regarding risk factors for schizophrenia, Table 2 reports on their effect size, and the credibility of evidence (Table 2). A meta-umbrella review (Arango et al. 2021) pooled evidence from umbrella reviews mapping risk factors of all mental disorders, including schizophrenia (Belbasis et al. 2018; Radua et al. 2018). We updated that meta-umbrella review. The study selection flow is reported in eFigure 1. Studies excluded after full-text assessment, with reason for exclusion, are reported in eTable 2. We identified recent umbrella reviews on psychological trauma, unsaturated fatty acids and cannabis use association with a range of mental disorders, including schizophrenia (Gao et al. 2022; Hogg et al. 2023; Solmi, De Toffol, et al. 2023), as well as a meta-analysis on prenatal and perinatal factors associated with schizophrenia published after the two former (meta-) umbrella reviews (Davies, Segre, et al. 2020; Gao et al. 2022; Solmi, De Toffol, et al. 2023), as well as one on risk factors within those meeting CHR-P criteria (Oliver, Reilly, et al. 2020). Across meta-analyses, several factors have been nominally significantly associated with psychosis, yet most meta-analytic evidence did not meet convincing or highly suggestive credibility according to established quantitative criteria (Ioannidis 2009; Fusar-Poli and Radua 2018; Solmi, Dragioti, Croatto, Radua, Borgwardt, Carvalho, Demurtas, Mosina, Kurotschka, Shin, et al. 2021). In more detail, as shown in Table 2, 146 factors were nominally associated with risk of psychosis, and specifically 37 were individual medical, psychiatric, psychological factors, 32 biomarkers, 16 related with pregnancy, 12 maternal and paternal factors, 10 ethnicity or migration-related factors, nine dealt with foetal growth and gestational age, six with labour season, labour complications, and delivery complications, six with individual infections, eight with individual or environmental stress and finally 10 risk factors were identified within subjects at CHR-P. Overall, only eight factors were supported by convincing evidence, namely UHR (OR = 9.32, 95%CI 4.91–17.32), black-Caribbean ethnicity in England (OR = 4.87, 95%CI 3.96–6.00), famine during pregnancy (OR = 1.61, 95%CI 1.51–1.71), birth weight below 2 kg (OR = 1.84, 95%CI 1.53–2.22), 2.5 kg (OR-1.53, 95%CI 1.31–1.78), 3 kg (OR = 1.23, 95%CI 1.15–1.31), and small for gestational age at birth (OR = 1.40, 95%CI 1.25–1.57), plus cannabis use in sensitivity analyses restricted to prospective studies. Additionally, in population-based studies, 14 factors met highly suggestive criteria, including childhood adversities in sensitivity analyses restricted to prospective studies (Arango et al. 2021; Solmi, De Toffol, et al. 2023). Finally, within CHR-P subjects no specific risk factor for transition to psychosis met convincing criteria.

Importantly, only three risk factors for schizophrenia-spectrum disorders had transdiagnostic salience across other mental disorders, according to TRANSD (Fusar-Poli, Solmi, et al. 2019) criteria. These are childhood adversities (shared with borderline personality disorder, and bipolar disorder), any psychological trauma (shared with bipolar disorder and anxiety disorder) and tobacco smoking (shared with opioid use disorder) (Arango et al. 2021), suggesting psychosis has some specific environmental risk factors compared with other disorders with only partial overlap.

#### 3.1.2. Definition of CHR-P, and assessment tools

The UHR concept, now more frequently defined as CHR-P, was introduced more than 25 years ago in Melbourne, Australia (Yung et al. 2005) (Table 3). Whilst the concept of 'prodrome' has prompted researchers to look for an 'at-risk' status with symptoms before the onset of schizophrenia, the concept of 'risk' status is different from 'prodromal' status. Whilst 'prodrome' is a retrospective and deterministic construct (i.e. the period before schizophrenia onset can only later be recognised as a prodrome). In contrast, 'risk' is a probabilistic one (i.e. those at risk have a certain probability of developing psychosis over time), that inherently implies the possibility of prevention. Hence, the concept of 'risk' also calls for caution in communicating and treating CHR-P status, as a substantial proportion – indeed, the majority – of individuals 'at risk' will not develop psychosis (Salazar de Pablo, Radua, et al. 2021).

The most widely accepted interviews to identify CHR-P are the CAARMS (Yung et al. 2005), and SIPS (Miller et al. 2003), that identify three CHR-P groups, namely Brief and Limited Intermittent Psychotic

**Table 3.** Main characteristics of comprehensive assessment of At-risk mental state and structured interview for prodromal symptoms interviews.

| | SIPS 5.6.1 (cOPS, pOPS) | CAARMS 2015 |
|---|---|---|
| Subscales/symptoms domains | P1: Unusual Thought Content/Delusional Ideas | P1: Unusual Thought Content |
| | P2: Suspiciousness/Persecutory Ideas | P2: Non-Bizarre Ideas |
| | P3: Grandiose Ideas | |
| | P4: Perceptual Abnormalities/Hallucinations | P3: Perceptual Abnormalities |
| | P5: Disorganised Communication | P4: Disorganised Speech |
| Severity | Seven levels (0–6) | Seven levels (0–6) |
| Frequency | Three levels (1–3) | Seven levels (0–6) |
| APS | | |
| Severity, frequency, functioning | Severity 3–5 plus Frequency 2 | *Subthreshold intensity*<br>Severity 3–5 (P1/2), 3–4 (P3), 4–5 (P4) plus Frequency 3–6<br>*OR*<br>*Subthreshold frequency*<br>Severity 6 (P1/2/4), 5–6 (P3) plus Frequency 3<br>AND<br>Both with SOFAS drop ≥ 30% sustained ≥1 month within the past year/<50 last 12 months |
| Symptoms to rate | Past month, in last 12 months | Last 12 months |
| Symptoms started | Started or worsened last 12 months, but could have been there even earlier | Up to five years earlier |
| BLIPS | | |
| Severity, frequency, functioning | Severity 6 plus Frequency 1 | Severity 6 (P1/2/4), 5–6 (P3) plus Frequency 4–6<br>AND<br>SOFAS drop ≥ 30% sustained ≥1 month within the past year/<50 last 12 months |
| Symptoms to rate | Past three months | Last 12 months |
| Symptoms started | Past three months | Up to five years earlier |
| Duration | Not more than three months | Not more than seven days |
| GRD | | |
| Criteria and functioning | Schizotypal personality disorder<br>OR<br>First-degree relative with psychotic disorder<br>AND<br>GAF drop ≥30% over the past month relative to 12 months prior | Schizotypal personality disorder<br>OR<br>First-degree relative with psychotic disorder<br>AND<br>SOFAS drop ≥ 30% sustained ≥1 month within the past year/<50 last 12 months |
| Psychosis | | |
| Psychosis criteria | Severity 6 plus Frequency 3<br>OR<br>Symptoms are seriously disorganising and dangerous | Severity 6 (P1/2/4), 5–6 (P3) plus Frequency 4–6 |
| Duration | NA | More than seven days |
| Exclusion criteria | | |
| Exclusion criteria | Previous diagnosis of psychosis, symptoms are seriously disorganising and dangerous | Previous diagnosis of psychosis (CAARMS or other sources) |
| | Symptoms are strongly connected with substance abuse | Symptoms strongly connected with hallucinogens, amphetamines, and cocaine (or other known to induce psychosis, excluding cannabinoids) |
| | Symptoms better explained by other disorder | |

*Legend.* SPS: Attenuated Psychotic Symptoms; BLIPS: Brief Limited Intermittent Psychotic Symptoms; CAARMS: Comprehensive Assessment of At-Risk Mental State; COPS: Criteria of Prodromal Syndromes; GRD: Genetic Risk and Deterioration; POPS: Presence of Psychotic Symptoms; SIPS: Structured Interview for Prodromal Symptoms. Edited from (Miller et al. 2003; Yung et al. 2005; Addington, Woods, et al. 2023).

Symptoms (BLIPS), Attenuated Positive Symptoms (APS), Genetic Risk and Deterioration (GRD) syndrome (Table 3). Briefly, BLIPS is defined by full positive psychotic symptoms that are, however, limited in frequency and duration. APS is defined by severity-subthreshold positive symptoms. GRD have schizotypal personality disorder or a first degree relative with psychosis as well as a recent drop in psychosocial functioning. Both CAARMS and SIPS should be administered to help-seeking subjects, and information gathered from the interview must be integrated with informants' input. Differences exist between CAARMS and SIPS on the maximum duration of subthreshold psychotic symptoms before defining a full-blown psychotic episode (Miller et al. 2003). Also, a non-negligible portion of CAARMS-defined BLIPS meets full psychosis criteria for SIPS (Miller et al. 2003; Fusar-Poli, Cappucciati, et al. 2016). Moreover, the two interviews assess differently concomitant substance use, as well as functional impairment for APS and BLIPS. Despite these and other differences (Table 3), CAARMS and SIPS have an overall agreement of 86–93% (Fusar-Poli, Cappucciati, et al. 2016) in determining CHR-P status, and the CONVERT tool (Fusar-Poli, Cappucciati, et al. 2016) is freely available to convert scores between the two instruments.

The difference between CHR-P (at-risk status) and brief psychotic disorder (full-blown schizophrenia-spectrum disorder) according to the DSM-5-TR (APA 2022) is

blurred, as the latter includes positive psychotic symptoms lasting from one day to one month (Miller et al. 2003), which overlaps with a subgroup of patients meeting CHR-P BLIPS criteria. Hence, differentiating between CHR-P and brief psychotic disorder is not always possible and at best challenging without using a semi-structured interview.

The study selection flow of the systematic review of novel psychometric tools for measuring CHR-P status is reported in eFigure 2. The systematic review identified four studies (Brady and Larrauri 2023; Addington, Woods, et al. 2024; Wannan et al. 2024; Woods SW et al. 2024) reporting on a newly developed instrument, the Positive Symptoms for CAARMS Harmonised with SIPS (PSYCHS), which integrates CAARMS and SIPS (eTable 3). In the PSYCHS, full harmonisation of CAARMS and SIPS has been achieved for rating positive symptoms severity and determining transition to psychosis, but not for assessing CHR-P subgroups, which still relies on separate SIPS or CAARMS criteria. The harmonisation process is described in more detail in eTable 3.

In CHR-P subjects, transition to frank psychosis can be assessed using either the CAARMS, SIPS, or PSYCHS, all of which require at least one positive psychotic symptom occurring several times a week. However, for determining transition, these measures differ in symptom duration (one week for the CAARMS and PSYCHS, one month for the SIPS) and waive duration and frequency if the symptom is imminently dangerous (PSYCHS) or either seriously disorganising or dangerous (SIPS), or in case a new or increased antipsychotic has been administered (CAARMS and PSYCHS).

In addition to the UHR/CHR-P criteria operationalised by CAARMS and SIPS, a complementary approach to identifying individuals with increased risk of psychosis has been developed based on the assessment of basic symptoms using the Schizophrenia Proneness Instrument—Adult (SPI-A) (Schultze-Lutter et al. 2012) and—Child and Youth (SPI-CY) (Schultze-Lutter et al. 2012). This approach focuses on self-experienced, subtle cognitive and perceptive disturbances, which are often subjectively distressing, preceding and accompanying attenuated or brief psychotic symptoms. However, meta-analytic evidence on the prognostic accuracy of such tools is lacking.

The systematic review with meta-analysis on the prognostic accuracy of a range of psychometric tools to measure CHR-P status showed that they have excellent prognostic accuracy in predicting psychosis in clinical samples at a mean follow-up of 34 months, i.e. AUC = 0.85 (95% CI: 0.81–0.88). More in detail, sensitivity was outstanding (0.93, 95% CI: 0.87–0.96), but specificity was poor (0.58, 95% CI: 0.50–0.66) (Oliver et al. 2022). In the discussion of that systematic review, authors indicated that CHR-P should be assessed in help-seeking, or risk-enriched populations only, because the prevalence of psychosis in the group undergoing CHR-P assessment determines CAARMS prognostic accuracy (Fusar-Poli, Schultze-Lutter, et al. 2016; Fusar-Poli, Sullivan, et al. 2019). Hence, administering CAARMS or SIPS to individuals who are not help-seeking, or outside of clinical services (such as screening in schools), is not useful in determining any risk of psychosis.

### *3.1.3. Biological correlates of clinical high risk of psychosis*

The study selection flow of the meta-umbrella on biological correlates in individuals at CHR-P is reported in eFigure 3 (Table 4). Studies excluded after full-text assessment, with reason for exclusion, are reported in eTable 4. The meta-umbrella review identified one umbrella review reporting on the biological alterations in subjects with CHR-P (Fusar-Poli et al. 2020) (Table 4). Biological alterations in CHR-P individuals resemble those consistently shown in individuals with schizophrenia. Compared with healthy controls, subjects at CHR-P have increased cortisol levels (Chaumette et al. 2016) as well as elevated IL-6 and IL-1beta (Park and Miller 2020).

The study selection flow of meta-analyses and large consortium brain imaging studies is reported in eFigure 4. Studies excluded after full-text assessment, with reason for exclusion, are reported in eTable 5. The umbrella review identified 17 eligible studies (Davis et al. 2014; Dutt et al. 2015; Erickson et al. 2016; Harrisberger et al. 2016; Merritt et al. 2016; Walter et al. 2016; Ding et al. 2019; Wenneberg et al. 2020; Del Fabro et al. 2021; Jalbrzikowski et al. 2021; Baldwin et al. 2022; Luna et al. 2022; Vissink et al. 2022; Zhao Y et al. 2022; Simmonite et al. 2023; Zeng et al. 2023; Allen et al. 2024) reporting on brain imaging findings in subjects with CHR-P, applying different techniques (Table 4). Among these, three studies (Jalbrzikowski et al. 2021; Baldwin et al. 2022; Allen et al. 2024) were from the ENIGMA consortium ($n = 2{,}577$–$3{,}169$). These studies reported on structural measures (brain volume, cortical thickness, surface area), functional measures (functional activity), and positron emission tomography or spectroscopy metrics (combined glutamate and glutamine, glutamate). In CHR-P subjects, there is converging evidence of a neuroprogressive process (Davis et al. 2014; Chaumette et al. 2016), evidenced by reduced brain volume, cortical thickness and surface area of the whole brain and specific areas (Jalbrzikowski

**Table 4.** Biological correlates of clinical high risk for psychosis.

| Biological factor | Source | Effect size* vs healthy controls |
|---|---|---|
| Inflammation vs HC | | |
| Cortisol (Chaumette et al. 2016) | MA ($k=8$, $n=1,060$)(Chaumette et al. 2016) | Hedge's $g=0.59$ (NA) |
| IL-6 (Park and Miller 2020) | MA ($k=5$, $n=229$) (Park and Miller 2020) | SMD = 0.31 (95%CI 0.02–0.59) |
| IL1-β (Park and Miller 2020) | MA ($k=2$, $n=74$) (Park and Miller 2020) | SMD=−0.66 (95%CI −1.27 to −0.05) |
| Neuroimaging# | | |
| Structural | | |
| Overall | | |
| Mean CT (Jalbrzikowski et al. 2021) | ENIGMA ($n=3,169$)(Jalbrzikowski et al. 2021) | Cohen's d=−0.18 (95%CI −0.25 to −0.11) |
| Estimated intracranial VOL (Jalbrzikowski et al. 2021) | ENIGMA ($n=3,169$)(Jalbrzikowski et al. 2021) | Cohen's d=−0.13 (95%CI −0.20 to −0.06) |
| Total SA (Jalbrzikowski et al. 2021) | ENIGMA ($n=3,169$)(Jalbrzikowski et al. 2021) | Cohen's d=−0.15 (95%CI −0.22 to −0.08) |
| Lower PBSI-SA (Baldwin et al. 2022) | ENIGMA ($n=2,644$)(Baldwin et al. 2022) | t(2642) = −5.39, $p<0.01$) |
| Lower PBSI-CT (Baldwin et al. 2022) | ENIGMA ($n=2,790$)(Baldwin et al. 2022) | (t(2788) = −9.11, $p<0.01$) |
| Lower PBSI-SV (Baldwin et al. 2022) | ENIGMA ($n=2,735$)(Baldwin et al. 2022) | (t(2733) = −4.34, $p<0.01$) |
| Global CT (Allen et al. 2024) | ENIGMA ($n=2577$)(Allen et al. 2024) | Cohen's d= <0.22 CI NA (decreased) |
| Infranormal global ADS (Allen et al. 2024) | ENIGMA ($n=2577$)(Allen et al. 2024) | $\chi^2=12.82$, FDR corrected $p=6.85\times10^{-4}$ |
| Infranormal SV ADS (Allen et al. 2024) | ENIGMA ($n=2577$)(Allen et al. 2024) | $\chi^2=5.68$, FDR corrected $p=0.02$ |
| Infranormal SA ADS (Allen et al. 2024) | ENIGMA ($n=2577$)(Allen et al. 2024) | $\chi^2=16.01$, FDR corrected $p=2.53\times10^{-4}$ |
| *Specific areas* | | |
| Left rostral anterior cingulate CT (Jalbrzikowski et al. 2021) | ENIGMA ($n=3,169$)(Jalbrzikowski et al. 2021) | Cohen's d=−0.11 (95%CI −0.18 to −0.04) |
| Bilateral posterior cingulate CT (Jalbrzikowski et al. 2021) (R) | ENIGMA ($n=3,169$)(Jalbrzikowski et al. 2021) | Cohen's d=−0.13 (95%CI −0.2 to −0.06) |
| Bilateral postcentral CT (Jalbrzikowski et al. 2021) (R) | ENIGMA ($n=3,169$) (Jalbrzikowski et al. 2021) | Cohen's d=−0.12 (95%CI −0.19 to −0.05) |
| Bilateral paracentral CT (Jalbrzikowski et al. 2021) (L) | ENIGMA ($n=3,169$) (Jalbrzikowski et al. 2021) | Cohen's d=−0.15 (95%CI −0.22 to −0.08) |
| Bilateral precentral CT (Jalbrzikowski et al. 2021) (LR) | ENIGMA ($n=3,169$) (Jalbrzikowski et al. 2021) | Cohen's d=−0.13 (95%CI −0.2 to −0.06) |
| Bilateral precuneus CT (Jalbrzikowski et al. 2021) (R) | ENIGMA ($n=3,169$) (Jalbrzikowski et al. 2021) | Cohen's d=−0.15 (95%CI −0.22 to −0.08) |
| Bilateral supramarginal CT (Jalbrzikowski et al. 2021) (L) | ENIGMA ($n=3,169$) (Jalbrzikowski et al. 2021) | Cohen's d=−0.11 (95%CI −0.18 to −0.04) |
| Left parahippocampal CT (Jalbrzikowski et al. 2021) | ENIGMA ($n=3,169$) (Jalbrzikowski et al. 2021) | Cohen's d=−0.13 (95%CI −0.2 to −0.06) |
| Bilateral insula CT (Jalbrzikowski et al. 2021) (L) | ENIGMA ($n=3,169$) (Jalbrzikowski et al. 2021) | Cohen's d=−0.17 (95%CI −0.24 to −0.1) |
| Bilateral medial orbitofrontal CT (Jalbrzikowski et al. 2021) (L) | ENIGMA ($n=3,169$) (Jalbrzikowski et al. 2021) | Cohen's d=−0.13 (95%CI −0.2 to −0.06) |
| Right lateral orbitofrontal CT (Jalbrzikowski et al. 2021) | ENIGMA ($n=3,169$) (Jalbrzikowski et al. 2021) | Cohen's d=−0.09 (95%CI −0.16 to −0.02) |
| Bilateral rostral middle frontal CT (Jalbrzikowski et al. 2021) (L) | ENIGMA ($n=3,169$) (Jalbrzikowski et al. 2021) | Cohen's d=−0.13 (95%CI −0.2 to −0.06) |
| Bilateral caudal middle frontal CT (Jalbrzikowski et al. 2021) (L) | ENIGMA ($n=3,169$) (Jalbrzikowski et al. 2021) | Cohen's d=−0.12 (95%CI −0.19 to −0.04) |
| Bilateral superior frontal CT (Jalbrzikowski et al. 2021) (L) | ENIGMA ($n=3,169$) (Jalbrzikowski et al. 2021) | Cohen's d=−0.11 (95%CI −0.18 to −0.04) |
| Bilateral fusiform CT (Jalbrzikowski et al. 2021) (L) | ENIGMA ($n=3,169$) (Jalbrzikowski et al. 2021) | Cohen's d=−0.17 (95%CI −0.24 to −0.1) |
| Bilateral superior parietal CT (Jalbrzikowski et al. 2021) (R) | ENIGMA ($n=3,169$) (Jalbrzikowski et al. 2021) | Cohen's d=−0.12 (95%CI −0.19 to −0.05) |
| Bilateral inferior parietal CT (Jalbrzikowski et al. 2021) (L) | ENIGMA ($n=3,169$) (Jalbrzikowski et al. 2021) | Cohen's d=−0.16 (95%CI −0.24 to −0.09) |
| Bilateral inferior temporal CT (Jalbrzikowski et al. 2021) (R) | ENIGMA ($n=3,169$) (Jalbrzikowski et al. 2021) | Cohen's d=−0.15 (95%CI −0.22 to −0.08) |
| Bilateral middle temporal CT (Jalbrzikowski et al. 2021) (R) | ENIGMA ($n=3,169$) (Jalbrzikowski et al. 2021) | Cohen's d=−0.18 (95%CI −0.26 to −0.11) |
| Right transverse temporal CT (Jalbrzikowski et al. 2021) | ENIGMA ($n=3,169$) (Jalbrzikowski et al. 2021) | Cohen's d=−0.11 (95%CI −0.18 to −0.04) |
| Bilateral superior temporal CT (Jalbrzikowski et al. 2021) (R) | ENIGMA ($n=3,169$) (Jalbrzikowski et al. 2021) | Cohen's d=−0.15 (95%CI −0.22 to −0.08) |
| Bilateral banks of the superior temporal sulcus CT (Jalbrzikowski et al. 2021) (R) | ENIGMA ($n=3,169$) (Jalbrzikowski et al. 2021) | Cohen's d=−0.13 (95%CI −0.2 to −0.06) |
| Bilateral lateral occipital CT (Jalbrzikowski et al. 2021) (R) | ENIGMA ($n=3,169$) (Jalbrzikowski et al. 2021) | Cohen's d=−0.16 (95%CI −0.23 to −0.09) |
| Bilateral medial prefrontal cortex CT (Zhao Y et al. 2022) | MA ($k=10$ $n=1,390$) (Zhao Y et al. 2022) | (z= −1.01, $p<0.001$) |
| Bilateral lateral ventricles VOL (Jalbrzikowski et al. 2021) (L) | ENIGMA ($n=3,169$) (Jalbrzikowski et al. 2021) | Cohen's $d=0.11$ (95%CI 0.04 to 0.18) |
| Hippocampus VOL (Harrisberger et al. 2016) | MA ($k=3$, $n=155$) (Harrisberger et al. 2016) | Hedge's g=−0.38 (95%CI −0.73 to −0.03) |
| Hippocampus VOL (R) (Jalbrzikowski et al. 2021) | ENIGMA ($n=3,169$) (Jalbrzikowski et al. 2021) | Cohen's d=−0.16 (95%CI −0.23 to −0.08) |
| Hippocampus VOL (R) (Walter et al. 2016) | MA ($n=1,429$) (Walter et al. 2016) | Hedge's g=−0.24, $p=0.0418$ |
| Hippocampus VOL (L) (Vissink et al. 2022) | MA ($k=7$, $n=1,088$) (Vissink et al. 2022) | Hedge's g=−0.26, (95% CI −0.49 to −0.02), $p=0.04$ |
| Hippocampus VOL (R) (Vissink et al. 2022) | MA ($k=7$, $n=1,088$) (Vissink et al. 2022) | Hedge's g=−0.33 (95% CI −0.60 to −0.07), $p=0.01$ |
| Thalamus VOL (Harrisberger et al. 2016) | MA ($k=3$, $n=155$) (Harrisberger et al. 2016) | Hedge's g=−0.60 (95%CI −0.96 to −0.25)** |
| Thalamus VOL (R) (Ding et al. 2019) | MA ($k=14$, $n=1,331$) (Ding et al. 2019) | $z=1.039$, (increased**) |
| Bilateral median cingulate VOL (Ding et al. 2019) | MA ($k=14$, $n=1,331$) (Ding et al. 2019) | $z=1.034$, (increased) |
| Right fusiform gyrus VOL (Ding et al. 2019) | MA ($k=14$, $n=1,331$) (Ding et al. 2019) | $z=1.051$, (increased) |
| Right gyrus rectus VOL (Ding et al. 2019) | MA ($k=14$, $n=1,331$) (Ding et al. 2019) | z=−2.109, (decreased) |
| Medial frontal gyrus VOL (Luna et al. 2022) | MA ($k=41$, $n=4,846$) (Luna et al. 2022) | Hedge's g=−0.28, $p<0.001$ |
| Right superior frontal gyrus VOL (Ding et al. 2019) | MA ($k=14$, $n=1,331$) (Ding et al. 2019) | z=−2.321, (decreased) |
| Left superior frontal gyrus VOL (Ding et al. 2019) | MA ($k=14$, $n=1,331$) (Ding et al. 2019) | z=−2.228, (decreased) |
| Left superior temporal gyrus VOL (Ding et al. 2019) | MA ($k=14$, $n=1,331$) (Ding et al. 2019) | $z=1.048$, (increased) |
| Lateral Ventricles VOL (Vissink et al. 2022) | MA ($k=3$, $n=841$) (Vissink et al. 2022) | Hedge's $g=0.17$ (95% CI 0.02 to 0.31), $p=0.02$ |

(*Continued*)

**Table 4.** Continued.

| Biological factor | Source | Effect size* vs healthy controls |
|---|---|---|
| Cerebrospinal VOL (Vissink et al. 2022) | MA ($k=4$, $n=922$) (Vissink et al. 2022) | Hedge's $g=0.21$ (95% CI 0.08 to 0.35), $p=0.002$ |
| Whole brain VOL (Vissink et al. 2022) | MA ($k=7$, $n=1,237$) (Vissink et al. 2022) | Hedge's g=−0.14 (95% CI −0.26 to −0.03), $p=0.02$ |
| Left entorhinal SA (Jalbrzikowski et al. 2021) | ENIGMA ($n=3,169$) (Jalbrzikowski et al. 2021) | Cohen's d=−0.09 (95%CI −0.16 to −0.02) |
| Right isthmus cingulate SA (Jalbrzikowski et al. 2021) | ENIGMA ($n=3,169$) (Jalbrzikowski et al. 2021) | Cohen's $d=0.09$ (95%CI 0.2 to 0.16) |
| Left pars opercularis SA (Jalbrzikowski et al. 2021) | ENIGMA ($n=3,169$) (Jalbrzikowski et al. 2021) | Cohen's d=−0.09 (95%CI −0.16 to −0.02) |
| Right pericalcarine SA (Jalbrzikowski et al. 2021) | ENIGMA ($n=3,169$) (Jalbrzikowski et al. 2021) | Cohen's d=−0.09 (95%CI −0.17 to −0.02) |
| Left supramarginal SA (Jalbrzikowski et al. 2021) | ENIGMA ($n=3,169$) (Jalbrzikowski et al. 2021) | Cohen's d=−0.11 (95%CI −0.18 to −0.04) |
| Left rostral anterior cingulate SA (Jalbrzikowski et al. 2021) | ENIGMA ($n=3,169$) (Jalbrzikowski et al. 2021) | Cohen's d=−0.12 (95%CI −0.19 to −0.04) |
| Right superior frontal SA (Jalbrzikowski et al. 2021) | ENIGMA ($n=3,169$) (Jalbrzikowski et al. 2021) | Cohen's d=−0.09 (95%CI −0.16 to −0.02) |
| Right inferior parietal SA (Jalbrzikowski et al. 2021) | ENIGMA ($n=3,169$) (Jalbrzikowski et al. 2021) | Cohen's d=−0.10 (95%CI −0.17 to −0.03) |
| Functional | | |
| Salience network connectivity (Del Fabro et al. 2021) | MA ($k=16$, $n=1,484$) (Del Fabro et al. 2021) | Hedge's g= −0.085, $p=0.012$ FDR corrected= 0.07 |
| Right precuneus (Luna et al. 2022) | MA ($k=55$, $n=3,096$) (Luna et al. 2022) | Hedge's g=−0.4, $p<0.001$ |
| Bilateral anterior cingulate cortex (Luna et al. 2022) | MA ($k=55$, $n=3,096$) (Luna et al. 2022) | Hedge's g=−0.33, $p<0.001$ |
| Right superior frontal gyrus (Dutt et al. 2015) | MA ($k=11$, n=NA) (Dutt et al. 2015) | $p<0.01$ (increased) |
| Right inferior frontal gyrus (Luna et al. 2022) | MA ($k=55$, $n=3,096$) (Luna et al. 2022) | Hedge's g=−0.34, $p<0.001$ |
| Left superior frontal gyrus (Luna et al. 2022) | MA ($k=55$, $n=3,096$) (Luna et al. 2022) | Hedge's g=−0.33, $p<0.001$ |
| Left medial frontal gyrus (Dutt et al. 2015) | MA ($k=15$, n=NA) (Dutt et al. 2015) | $p<0.01$ (decreased) |
| Right inferior parietal lobule (Dutt et al. 2015) | MA ($k=15$, n=NA) (Dutt et al. 2015) | $p<0.01$ (decreased) |
| Left superior temporal gyrus (Dutt et al. 2015) | MA ($k=11$, n=NA) (Dutt et al. 2015) | $p<0.01$ (increased) |
| Medial prefrontal cortex and anterior cingulate cortex activation in response to monetary stimuli (Zeng et al. 2023) | MA ($k=13$, $N=744$) (Zeng et al. 2023) | SMD= 1.330, $p<0.001$ (increased) |
| Left cerebellum and parahippocampal gyrus activation in response to monetary stimuli (Zeng et al. 2023) | MA ($k=13$, $N=744$) (Zeng et al. 2023) | SMD= −2.051, $p<0.001$ (decreased) |
| Right supramarginal gyrus activation in response to monetary stimuli (Zeng et al. 2023) | MA ($k=13$, $N=744$) (Zeng et al. 2023) | SMD= −1.775, $p<0.001$ (decreased) |
| Right insula and putamen activation in response to monetary stimuli (Zeng et al. 2023) | MA ($k=13$, $N=744$) (Zeng et al. 2023) | SMD= −1.485, $p<0.001$ (decreased) |
| **Mismatch negativity** | | |
| Mismatch negativity (Erickson et al. 2016) | MA ($k=16$, N=NA) (Erickson et al. 2016) | Cohen's $d=0.40$ (95%CI 0.23 to 0.58) (increased) |
| PET/MRS | | |
| Medial frontal Glx (MRS) (Merritt et al. 2016) | MA ($k=8$, $N=386$) (Merritt et al. 2016) | Hedge's $g=0.26$ (95%CI 0.05 to 0.46) |
| Frontal Glx (MRS) (Wenneberg et al. 2020) | MA ($k=4$, $N=140$) (Wenneberg et al. 2020) | SMD= 0.55 (95% CI 0.21 to 0.89), $p=0.001$ (increased) |
| Thalamus glutamate (MRS) (Wenneberg et al. 2020) | MA ($k=3$, $N=218$) (Wenneberg et al. 2020) | SMD= −0.5 (95% CI −0.78 to −0.23), $p<0.001$ |

*Legend.* ADS: average deviation score; CT: cortical thickness; Glx: combined glutamate and glutamine; IL: interleukin; MA: meta-analysis; MRS: proton magnetic resonance spectroscopy; PBSI: person-based similarity index; PET: positron emission tomography; SMD: standardised mean difference; VR: Variability ratio; *Positive values indicate higher levels in CHR;**, opposite findings from two works on thalamus; # when bilateral, left or right side with largest difference is indicated [(L) or (R)], and reported. Edited from (Davis et al. 2014; Dutt et al. 2015; Chaumette et al. 2016; Erickson et al. 2016; Harrisberger et al. 2016; Merritt et al. 2016; Walter et al. 2016; Ding et al. 2019; Fusar-Poli Paolo et al. 2020; Park and Miller 2020; Wenneberg et al. 2020; Del Fabro et al. 2021; Jalbrzikowski et al. 2021; Baldwin et al. 2022; Luna et al. 2022; Vissink et al. 2022; Zhao Y et al. 2022; Zeng et al. 2023; Allen et al. 2024).

et al. 2021); however, the effect sizes ranges from very small to small (Cohen's $d=0.13$–$0.22$) (Allen et al. 2024). Among specific brain regions, alterations emerged for some areas that were confirmed across more than one metric, that were replicated in more than one study on the same metric, or that had a medium effects size. Compared with healthy controls, CHR-P subjects exhibit prominently altered frontal lobes; reduced volume in bilateral superior frontal gyri (Ding et al. 2019), reduced cortical thickness (Jalbrzikowski et al. 2021), and reduced surface area (Jalbrzikowski et al. 2021), asymmetric altered activation (right increased, left decreased) (Dutt et al. 2015; Luna et al. 2022), and increased combined glutamate plus glutamine levels (Merritt et al. 2016; Wenneberg et al. 2020). Bilateral medial prefrontal cortex has reduced cortical thickness (Zhao Y et al. 2022) and increased motivational-related activation during reward anticipation (Zeng et al. 2023). Also, the right inferior parietal lobule shows decreased cortical thickness (Jalbrzikowski et al. 2021), surface area (Jalbrzikowski et al. 2021) and function (Dutt et al. 2015). In addition, the left superior temporal gyrus shows increased volume (Ding et al. 2019), reduced cortical thickness (Jalbrzikowski et al. 2021), and increased activation (Dutt et al. 2015). Furthermore, the left anterior cingulate has reduced cortical thickness (Jalbrzikowski et al. 2021), reduced surface area (Jalbrzikowski et al. 2021), and reduced activation in resting state (Luna et al. 2022), whereas there is increased activation in the bilateral anterior cingulate

cortex during reward anticipation (Zeng et al. 2023). Among subcortical structures, a number of studies reported a reduced volume of both the right hippocampus (Harrisberger et al. 2016; Walter et al. 2016; Jalbrzikowski et al. 2021) and the left hippocampus (Harrisberger et al. 2016; Vissink et al. 2022). The largest difference has been reported for the thalamus, which has reduced volume in CHR-P subjects (medium effect size) (Harrisberger et al. 2016), as well as reduced glutamate levels (Wenneberg et al. 2020). Lastly, bilateral lateral ventricles showed increased volume in two studies (Jalbrzikowski et al. 2021; Vissink et al. 2022). Mismatch negativity was increased in CHR-P compared with healthy controls (Erickson et al. 2016). Apart from these areas where brain alterations were confirmed across different reports or measures, all other differences were largely non-significant, not replicated, and virtually all of them had a very small effect size (Cohen's d/Hedge's $g < 0.2$).

### 3.1.4. Comorbid mental disorders of CHR-P

Subjects meeting CHR-P criteria frequently have poor functioning, or a drop in functioning (at least according to CAARMS), and present with frequent symptoms of or full-blown comorbid mental disorders (Table 5). In a recent meta-analysis (Solmi, Soardo, et al. 2023), that pooled data from 312 observational and interventional studies that reported comorbid mental disorders in almost 35,000 CHR-P subjects, 75.7% of subjects met criteria for at least one non-psychotic disorder (Table 5). The most frequent disorders were anxiety/mood disorders (60.1%), any mood disorders (43.7%), any depressive disorder/episode (39.3%), any anxiety disorder (33.7%), major depressive disorder (31.1%), any trauma-related disorder (29.4%), any personality disorder (23.3%), any pervasive developmental disorder (around 14.8%), neurotic, stress-related and somatoform disorders (around 14.2%), cannabis use disorder (13%), schizotypal personality disorder (12.5%), attention-deficit/hyperactivity disorder (12.5%), any behavioural disorder (12.5%), pervasive developmental disorder not otherwise specified (12.1%), social anxiety disorder (11.8%), any substance use disorder (11.8%), phobias (11.5%), avoidant personality disorder (10.5%), borderline personality disorder (10.4%), and other disorder in less than 10% of study participants. While the vast majority of these comorbid disorders do not seem to be associated with functioning (i.e. aggravate or mitigate functioning impairment already present with CHR-P status), some of them are (Solmi, Soardo, et al. 2023). Somatoform disorder, alcohol use disorder, and schizotypal personality disorder (in descending order of magnitude) are associated with a more severe impairment of functioning, whilst dysthymia and generalised anxiety disorder (again in descending order of magnitude) with a less severe impairment of functioning. Also, importantly, according to the same meta-analysis (Solmi, Soardo, et al. 2023), comorbid mood disorder, generalised anxiety disorder and agoraphobia are associated with lower odds of transition to psychosis. After meeting CHR-P criteria, up to eight years of follow-up, rates of any non-psychotic disorders decrease somewhat, yet remain high, being still present in >50% of subjects meeting CHR-P criteria at baseline.

Given the high proportion of CHR-P subjects with comorbid mental disorders, the clinical needs of these subjects go beyond the prevention of psychosis.

**Table 5.** Course and impact of concomitant mental disorders in subjects at CHR-P.

| Course of concomitant mental disorders over time in CHR-P subjects |
|---|
| Over 75% of CHR-P subjects have a concomitant DSM/ICD mental disorder |
| Most frequent concomitant mental disorders at baseline CHR-P assessment are: |
| Any mood disorder, around 43% |
| Depressive disorder, around 39% |
| Anxiety disorders, around 33% |
| Any trauma-related disorder, around 29% |
| Personality disorders, around 23% |
| Up to eight years after meeting CHR-P status criteria, a comorbid mental disorder is still present in more than 50% of subjects |
| Impact of concomitant mental disorders on functioning in CHR-P subjects |
| Somatoform disorder, alcohol use disorder, and schizotypal personality disorder are associated with worse functioning impairment (in descending order of magnitude) |
| Dysthymia and generalised anxiety disorder moderate a less severe impairment of functioning (in descending order of magnitude) |
| Impact of comorbid mental disorders on transition to psychosis in CHR-P subjects |
| Comorbid mood disorder, generalised anxiety disorder and agoraphobia lower the odds of transition to psychosis. |

*Legend.* DSM, Diagnostic and Statistical Manual; ICD, International Classification of Diseases. Edited from (Solmi, Soardo, et al. 2023).

### 3.1.5. Age at onset of psychosis, epidemiology of transition from CHR-P to psychosis, psychosis prediction models, and ethical considerations to inform clinical implementation of psychosis prevention

Regarding age at onset of psychosis, according to the largest meta-analysis conducted so far on the age at onset of mental disorders (Solmi, Radua, et al. 2022), the proportion of individuals with onset of a schizophrenia spectrum disorder before the age of 14, 18, 25 was 3%, 12.3%, 47.85%, supporting that the age eligibility criteria for psychosis prevention programs should be age 14 (Table 6).

**Table 6.** Epidemiology of transition to psychosis, risk estimates, and ethical considerations.

| Epidemiology of transition to psychosis | |
|---|---|
| Subjects at CHR-P have increased risk of transition to psychosis | The prevalence of schizophrenia is around 1% in the general population. The prevalence of CHR-P is 1.7% and 19.2% in the general population and in clinical samples, respectively. |
| | The rate of transition to psychosis in CHR-P subjects is as high as 8% at 6 months, reaching 29% at 4 years, then plateauing and reaching 35% at 10 years from CHR-P baseline assessment, but lower for children and adolescents |
| Estimating risk of transition to psychosis | |
| Tools | The two most employed diagnostic tools to assess early psychosis are CAARMS and SIPS, with good prognostic performance |
| | In clinical centres where CAARMS or SIPS/SOPS are not used, an individualised transdiagnostic risk calculator has been recently developed employing electronic health information. This tool can be used not only in CHR-P patients, but also in any other individual with non-psychotic psychiatric disorder. |
| Population | Assessment of CHR-P status or risk of psychosis should only be assessed in help-seeking non-psychotic (sub) clinical population, as the prognostic accuracy of CAARMS and SIPS/SOPS is poor if applied to the general population. |
| Validate prognostic/prediction models | Models should be developed, validated internally, and replicated in external samples to ensure generalisability. |
| | Models' prognostic/prediction accuracy must be determined through discrimination values (Harrel C index or Area-Under-the Curve, sensitivity, specificity), calibration (regression slope of prognostic index), overall performance ($R^2$, Brier Score), in longitudinal cohort studies. |
| Risk calculators candidates | Multiple risk calculators have been developed, which should be updated with evidence on additional risk factors (see Table 2). |
| Key ethical principles | |
| Autonomy | The right for an individual to make their own choice |
| Beneficence | The principle of acting with the best interest of the other in mind |
| Non-maleficence | The principle that 'above all, do no harm' |
| Justice | Fairness and equality among individuals |
| Explainability/interpretability | Why a clinical prediction model arrives at an output/prediction |
| Implementation of key ethical principles, and reasons | |
| Keep a human component in the risk assessment and communication | Promote social interactions, promoting human-to-human interaction in the risk estimate, avoiding social isolation |
| | Involve the user in the critical interpretation of risk estimate, to avoid acritical acceptance of automated outputs |
| | Allow users to benefit from risk estimates, accepting and preventing the risk of automation distrust deriving from the absence of human-to-human interaction |
| | Always ensure accountability, which is complicated in fully automated risk estimates |
| | Mitigate digital divide, i.e. gap in access to preventive care for those subjects with limited digital literacy or limited access to digital devices |
| | Ask users if they want to be informed about the risk estimate |
| Ensure validity and representativeness | Only use validated clinical prediction models (see above), to avoid structural bias and over-optimism |
| | Ensure that clinical prediction models have been validated in populations representative of users (under- or over-representation of minorities limits generalisability) |
| Ensure transparency and reproducibility | Use glass-box clinical prediction models with transparent and reproducible algorithms, instead of black-box 'obscure' machine learning protocols |
| Training of operators | Offer CHR-P assessment tools training to operators |
| | Offer clinical prediction model training to operators, so all variables in the clinical prediction model are accurately collected, beyond other sources of incentives that could bias diagnostic codes |
| | Train in ethical communication of risk |

*Legend.* Edited from (Fusar-Poli, Rutigliano, Stahl, Davies, Bonoldi, et al. 2017; Fusar-Poli, Rutigliano, Stahl, Davies, De Micheli, et al. 2017; Fusar-Poli et al. 2018; Fusar-Poli, Werbeloff, et al. 2019; Puntis et al. 2021; Salazar de Pablo, Studerus, et al. 2021; Salazar de Pablo, Woods, et al. 2021; Fusar-Poli, Manchia, et al. 2022; Meehan et al. 2022).

A recent meta-analysis pooled data from 130 studies and 9,222 individuals (Salazar de Pablo, Radua, et al. 2021). The cumulative transition risk from CHR-P to psychosis was 8% at 6 months, 14% at 1 year, 17% at 1.5 years, 20% at 2 years, 25% at 2.5 years, 27% at 3 years, 28% at 3.5 years, 29% at 4 years, and 35% at 10 years (Salazar de Pablo, Radua, et al. 2021) (Table 6). Moreover, a lower proportion of female individuals (β = −0.02; 95% CI: −0.04 to −0.01) and a higher proportion of BLIPS (β = 0.02; 95% CI: 0.01–0.03) were associated with higher transition risk. Also, across CHR-P cohorts, higher age has been identified as a risk factor for transition to psychosis (Fusar-Poli et al. 2012). Indeed, risk for transition to psychosis is lower in children and adolescents fulfilling CHR-P criteria, being 9.5% at 1 year, 12.1% at 2 years and only 16.1% at ≥5 years (Lång et al. 2022). The lower conversion rates to psychosis compared to adults are likely due to the fact that attenuated positive symptoms are less specific before adulthood, possibly being associated with internalising, externalising, substance use and personality disorder traits or diagnoses that might also emerge around the same age (Kelleher, Murtagh, et al. 2012; Gerstenberg et al. 2015; Schimmelmann et al. 2015; Gerstenberg et al. 2016). Additionally, even full psychotic symptoms appear to be less specific in youth. The meta-analytically determined median prevalence of psychotic symptoms – predominantly auditory hallucinations – is as high as 17% among children aged 9–12 years and much lower, i.e. 7.5%, among adolescents aged 13–18 years (Kelleher, Connor, et al. 2012) where epidemiologically the risk for psychosis

should be higher (Solmi, Radua, et al. 2022). Nevertheless, when measured in the same study with homogeneous definitions and tools, the duration of untreated psychosis appears to be three times as long in adolescents than adults with first episode psychosis (5.4 ± 3.1 vs 18.7 ± 6.2 months (Stentebjerg-Olesen et al. 2016)), highlighting the need to focus on psychosis prevention in youth too. The risk of transition to psychosis can be measured with two different yet complementary approaches in subjects who are help-seeking or assessed in a clinical context. A first possibility is to administer a clinical interview to assess whether a subject meets CHR-P criteria. CAARMS's area under the curve (AUC) at 2 years is 0.79 (Oliver et al. 2018), with a sensitivity and specificity of 83% and 74% at 6 months (Yung et al. 2005), respectively. SIPS had a sensitivity of 100%, as well as a specificity of 71% at six months (Miller et al. 2003) follow-up. A second approach to quantify the risk of transition to psychosis is to use risk calculators. Risk calculators for psychosis are among the most valid clinical prediction models in psychiatry, and can be used by healthcare professionals, regardless of previous administration of CAARMS or SIPS, since they rely on demographic characteristics and clinical diagnoses (Table 6). The use of calculators might be a more feasible approach in settings or time periods with insufficient staff to administer CAARMS or SIPS. The two approaches can also be combined, as the risk of transition to psychosis is not the same across all individuals with CHR-P. Clinical prediction models are crucial for developing and implementing precision psychiatry, but methodological and ethical guidance should be followed. Regarding the methodological standards for prediction models, a large sample size is needed to have a sufficient number of events (at least 100), and an appropriate events/model variables ratio (ideally at least 20 events per model variable, i.e. event per variable, EPV), to protect from biased results and overfitting (Meehan et al. 2022). Also, the variables/predictors that compose the model should be identified *via* systematic review of the literature, and should be considered all together in multivariable models. Furthermore, after its development within a given sample, each model should be validated internally and externally in new cohorts of individuals (Meehan et al. 2022). The validity of each prediction model should be measured with discrimination metrics, calibration, and overall performance (Table 6) (Fusar-Poli et al. 2018). Finally, the clinical impact of each model should be measured with simulation studies or real-world experimental studies (Meehan et al. 2022). We account for these and other methodological aspects of prediction typically measured with the Prediction model Risk Of Bias Assesment Tool (PROBAST) (Wolff et al. 2019), updating a previous systematic review focusing on prediction of psychosis. The study selection flow of the updated systematic review (Salazar de Pablo, Studerus, et al. 2021) on prediction and prognosis models with proper internal or external validation specifically focusing on CHR-P status and prediction of psychosis onset, is reported in eFigure 5. Out of 1742 hits, we ultimately identified 40 additional studies since previous reviews (Fusar-Poli, Stringer, et al. 2019; Osborne and Mittal 2019; Zarogianni et al. 2019; Zhang et al. 2019; Bourgin et al. 2020; Collin et al. 2020; Oliver, Wong, et al. 2020; Perkins et al. 2020; Raket et al. 2020; Studerus et al. 2020; Yassin et al. 2020; Dickens et al. 2021; Grent-'t-Jong et al. 2021; Haining et al. 2021; Hauke et al. 2021; Irving et al. 2021; Koutsouleris et al. 2021; Mongan et al. 2021; Puntis et al. 2021; Worthington et al. 2021; Antonucci et al. 2022; Dwyer et al. 2022; Koutsouleris et al. 2022; Lee et al. 2022; Li Z et al. 2022; Moore et al. 2022; Sullivan et al. 2022; Worthington et al. 2022; Doborjeh et al. 2023; Iftimovici et al. 2023; Loch et al. 2023; Lyu et al. 2023; Mondelli et al. 2023; Argolo et al. 2024; Byrne et al. 2024; Hartmann et al. 2024; Kizilay et al. 2024; Krakowski et al. 2024; Reinen et al. 2024; Sprungli-Toffel et al. 2024; Zhu Y et al. 2024), highlighting an increased research interest in the field. Studies excluded after full-text assessment, with reason for exclusion, are reported in eTable 6. The systematic review found that all prediction models published in the field of CHR-P status and prediction of psychosis onset were at high risk of bias according to PROBAST. The largest source of bias was the analysis domain. A critical factor was that studies tended to include too many variables per number of events, or even completely neglected this aspect, not even reporting information to assess EPV (Fusar-Poli et al. 2018). Another critical factor was the inclusion of a component of the outcome (i.e. positive symptoms) among predictors. Only 11 studies externally validated models in a sample with ≥100 events (Fusar-Poli et al. 2018). Finally, only three prediction models (Fusar-Poli, Rutigliano, Stahl, Davies, Bonoldi, et al. 2017; Raket et al. 2020; Krakowski et al. 2024) assessed clinical utility, applying decision-curve analyses, aiming to measure the potential 'net benefit' over routine practice (Fusar-Poli et al. 2018). Hence, despite methodological limitations in the field of mental health, in psychiatry the field of prevention of psychosis is the one where the most progress has been made in terms of clinical prediction. Nevertheless, the

potential implementation of prediction models requires ethical considerations.

Regarding the ethical considerations around risk prediction and communication, a recent review and consensus statement involving multidisciplinary stakeholders led by the European College of Neuropsychopharmacology Prevention of Severe Mental Disorders (PSMD) Cluster and funded by the European Brain Research Area (EBRA) provided a unique ethical insight on how researchers and clinicians should assess and communicate risk calculated with a novel clinical prediction model (Fusar-Poli, Manchia, et al. 2022). Such an ethical framework applies well to assessing and communicating the risk of transition to psychosis in subjects meeting CHR-P criteria. Research and clinical practice should always follow key ethical principles, namely autonomy, beneficence, non-maleficence, justice, and explainability/interpretability. These principles should guide the clinical implementation of precision psychiatry, risk assessment and communication. Briefly, some overarching clinically relevant principles are necessary for an ethical implementation of risk calculations and precision psychiatry in the field of prevention of psychosis (and beyond). These include offering human-to-human interaction to users, only relying on validated clinical prediction models that must be transparent and reproducible and administered by appropriately trained operators. The definition of ethical principles, and the reasons for their clinical implementation are described in more detail in Table 6.

### *3.1.6. Randomised controlled trials to prevent psychosis*

The study selection flow of the systematic review of RCTs in subjects meeting CHR-P status criteria is reported in eFigure 6 (Table 7). Out of initial 1207 hits, we ultimately included 44 RCTs reported across 70 publications (McGorry et al. 2002; Morrison et al. 2004; McGlashan et al. 2006; Nordentoft et al. 2006; Morrison et al. 2007; Ruhrmann et al. 2007; Amminger et al. 2010; Addington et al. 2011; Bechdolf et al. 2011; Yung et al. 2011; Bechdolf et al. 2012; Morrison et al. 2012; van der Gaag et al. 2012; McGorry et al. 2013; Woods SW et al. 2013; Miklowitz et al. 2014; Kantrowitz et al. 2015; Piskulic et al. 2015; Ising et al. 2016; Loewy et al. 2016; Stain et al. 2016; Albert et al. 2017; Bechdolf et al. 2017; Cadenhead K et al. 2017; Choi et al. 2017; McGorry et al. 2017; Woods S et al. 2017; Bhattacharyya et al. 2018; Mossaheb, Papageorgiou, et al. 2018; Mossaheb, Schäfer, et al. 2018; Nelson et al. 2018; Piskulic et al. 2018; TD et al. 2018; Berger et al. 2019; Bolt et al. 2019; Cadenhead KS et al. 2019; Davies, Paloyelis, et al. 2019; Davies, Rutigliano, et al. 2019; Pozza et al. 2019; Wessels et al. 2019; Wilson et al. 2019; Alqarni et al. 2020; Amminger et al. 2020; Appiah-Kusi et al. 2020; Davies, Wilson, et al. 2020; Glenthøj et al. 2020; Kristensen et al. 2020; Mallawaarachchi et al. 2020; Schmidt A et al. 2020; Glenthøj et al. 2021; Li H et al. 2021; Myin-Germeys et al. 2021; Pozza et al. 2021; Rinne et al. 2021; Tsai et al. 2021; Friedman-Yakoobian et al. 2022; Addington, Liu, et al. 2023; Bechdolf et al. 2023; Davies et al. 2023; McGorry et al. 2023; Tang et al. 2023; Waite et al. 2023; Zhao J et al. 2023; Zhu H et al. 2023; Davies, Bossong et al. 2024; Davies, Martins et al. 2024; Livingston et al. 2024; Qurashi et al. 2024; Wasserthal et al. 2024) with publicly available results, plus 30 RCTs that are still ongoing or for which results are not publicly available. Studies excluded after full-text assessment, with reason for exclusion, are reported in eTable 7. Details of the included RCTs are reported in Table 7, while characteristics of RCTs still ongoing or for which no results are available are described in eTable 8.

Among the RCTs that reported results, eight studies focused on cognitive therapy or CBT or CBT-informed interventions (Morrison et al. 2004; 2007; Addington et al. 2011; Morrison et al. 2012; van der Gaag et al. 2012; Ising et al. 2016; Stain et al. 2016; Pozza et al. 2019, 2021; Addington, Liu, et al. 2023; Waite et al. 2023), 14 on other psychosocial interventions (Nordentoft et al. 2006; Bechdolf et al. 2012; Miklowitz et al. 2014; Piskulic et al. 2015; Loewy et al. 2016; Albert et al. 2017; Choi et al. 2017; Piskulic et al. 2018; TD et al. 2018; Wessels et al. 2019; Glenthøj et al. 2020; Kristensen et al. 2020; Glenthøj et al. 2021; Li H et al. 2021; Myin-Germeys et al. 2021; Rinne et al. 2021; Tsai et al. 2021; Friedman-Yakoobian et al. 2022; Zhao J et al. 2023), 16 on biological interventions (McGlashan et al. 2006; Ruhrmann et al. 2007; Amminger et al. 2010; Woods SW et al. 2013; Kantrowitz et al. 2015; Cadenhead K et al. 2017; Woods S et al. 2017; Bhattacharyya et al. 2018; Mossaheb, Papageorgiou, et al. 2018; Mossaheb, Schäfer, et al. 2018; Cadenhead KS et al. 2019; Davies, Paloyelis, et al. 2019; Davies, Rutigliano, et al. 2019; Wilson et al. 2019; Appiah-Kusi et al. 2020; Davies, Wilson, et al. 2020; Schmidt A et al. 2020; Davies et al. 2023; Tang et al. 2023; Zhu H et al. 2023; Davies, Bossong et al. 2024; Davies, Martins et al. 2024; Livingston et al. 2024; Qurashi et al. 2024), and six on combined (i.e. psychosocial plus biological) interventions (McGorry et al. 2002; Bechdolf et al. 2011; Yung et al. 2011; McGorry et al. 2013; Bechdolf et al. 2017; McGorry et al. 2017; Nelson et al. 2018; Berger et al. 2019; Bolt et al. 2019; Alqarni et al. 2020; Amminger et al. 2020; Mallawaarachchi et al. 2020;

**Table 7.** Individual randomised controlled trials to prevent psychosis in people at clinical high risk for psychosis.

| Author, year/RCT/RoB | Centre | Referrals | CHR-P definition | N | Age | Blinding | Intervention | Control | Duration* | Primary and other outcomes | Superior treatment# | Improve from baseline within group |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cognitive therapy or cognitive-behavioural therapy | | | | | | | | | | | | |
| (Addington et al. 2011)<br>High RoB | PRIME Clinic, CAMH, Toronto, Canada | Primary care (GP), mental health specialists, general population (radio, public transport, newspapers) | SIPS | 51<br>27/ 24 | 21<br>14 to 30 | SB | Problem-focused CBT (up to 20 sessions) (audiotaped for treatment fidelity) (French and Morrison 2004) | Supportive therapy | 6M | **Transition**, positive, negative, depressive, anxiety symptoms, social functioning, drop-out | None | Problem-focused CBT (positive, anxiety symptoms)<br>Supportive therapy (positive, depressive, anxiety symptoms) |
| (Addington, Liu, et al. 2023)<br>NCT02234258<br>Some concerns | University of Calgary, Canada; University of California, San Diego, US; Zucker Hillside Hospital, New York, US | Health care providers, educators, social service agencies and self-referrals | SIPS | 152<br>70/ 82 | 17.36<br>17.49<br>12 to 13 | SB | Cognitive-Behavioural Social Skills Training (CBT SST) | Supportive therapy | 4,5M | **Global social functioning,** defeatist beliefs | None | CBT SST (defeatist beliefs, social functioning, social self-efficacy)<br>Supportive therapy (positive, negative, depressive, anxiety symptoms) |
| (Morrison et al. 2004; 2007)<br>High RoB | NR | Primary care, student counselling services, emergency departments, mental health specialists, voluntary sector agencies | PACE<br>PANSS<br>BPRS | 60<br>37/23 | 22<br>16 to 36 | SB | Cognitive therapy + monitoring | Monitoring | 12M | **Transition**, positive symptoms, functioning, distress | Cognitive therapy (**Transition)** | NP |
| (Morrison et al. 2012)<br>High RoB | Manchester, Birmingham/ Worcestershire, Glasgow, Cambridgeshire, Norfolk, UK | Primary and secondary healthcare professionals | CAARMS | 288<br>144/144 | 20.74<br>14 to 35 | SB | Cognitive therapy + monitoring | Monitoring | 12M | **Transition**, **severity of symptoms, distress**, emotional dysfunction, quality of life | Cognitive therapy (severity of symptoms) | NR |
| (Pozza et al. 2019, 2021)<br>High RoB | Florence, Prato, Italy | Five community mental health centres | CAARMS | 58<br>29/29 | 25.41 (CBT)<br>26 (control)<br>16 to 35 | SB | CBT | Individual supportive sessions | 7 M | **Transition,**anxiety symptoms, depressive symptoms | CBT (**Transition,** depressive symptoms, anxiety symptoms) | CBT (depressive symptoms, anxiety symptoms)<br>Individual supportive sessions (depressive symptoms, anxiety symptoms) |
| (Stain et al. 2016)<br>ANZCTR 12606000101583<br>High RoB | Psychological Assistance Service, Newcastle; Centre for Rural and Remote Mental Health, Orange, Australia | Primary healthcare services, self-referrals, community mental health services, community adolescent teams, counselling services, youth-related services | CAARMS<br>SCID<br>K-SADS | 57<br>30/27 | 16.5<br>14 to 30 | SB | CBT | Non Directive Reflective Listening | 18M | **Transition**, functioning, distress, symptom severity, quality of life | Non Directive Reflective Listening (distress) | CBT (symptom severity)<br>Non Directive Reflective Listening (symptom severity, distress) |

(*Continued*)

**Table 7.** Continued.

| Author, year/RCT/RoB | Centre | Referrals | CHR-P definition | N | Age | Blinding | Intervention | Control | Duration* | Primary and other outcomes | Superior treatment# | Improve from baseline within group |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (van der Gaag et al. 2012; Ising et al. 2016)<br>ISRCTN21353122<br>High RoB | Mental Health Centre PsyQ Haaglanden, the Hague, Academic Medical Centre and Mental Health Centre PsyQ, Amsterdam, Mental Health Centre Rivierduinen, Leiden Mental Health Institute Friesland, Friesland, Amsterdam<br>. | General practitioners | CAARMS<br>Prodromal Questionnaire | 201<br>97/104 | 22.9 (experimental)<br>22.6 (control)<br>14 to 35 | SB | CBT for ultra high risk patients with Treatment as usual | Treatment as usual | 24M | **Transition**, depression, anxiety, quality of life, functioning, beliefs about illness | CBT UHR (**Transition**) | CBT for ultra-high risk with Treatment as usual (depression, anxiety, distress)<br>Treatment as usual (anxiety, depression) |
| (Waite et al. 2023)<br>ISRCTN85601537<br>Low RoB | Oxford Health NHS Foundation Trust, Berkshire Healthcare NHS Foundation Trust, England, UK | Mental health services | CAARMS | 40<br>21/19 | 16.9<br>14 to 23 | SB | SleepWell therapy with Treatment as usual | Treatment as usual | 3M | **Insomnia severity,** psychotic experiences, depressive, anxiety symptoms | SleepWell therapy+Treatment as usual (**Insomnia severity**) | NR |
| **Other psychosocial interventions** | | | | | | | | | | | | |
| (Bechdolf et al. 2012; Wessels et al. 2019)<br>NCT00204087<br>High RoB | Department of Psychiatry and Psychotherapy in Cologne, Bonn, Dusseldorf, Munich, Germany | Primary care, mental health specialists, counsellors | ERIraos, IRAOS | 128<br>63/65 | 26.0<br>NA | OL | Integrated psychological intervention (combination of CBT/ST/CCRT/ EDU)(A et al. 2010) | Supportive counselling | 12M | **Transition**, treatment response | Integrated psychological intervention (**transition**) | NP |
| (Nordentoft et al. 2006)<br>High RoB | Copenhagen Hospital Corporation and Psychiatric Hospital Aarhus, Denmark (Petersen et al. 2005) | All inpatient and outpatient mental health services in Copenhagen (Copenhagen Hospital Corporation) and Aarhus county | ICD-10 (Schizotypal disorder) | 79<br>42/37 | 24.9<br>18 to 45(Petersen et al. 2005) | OL | Integrated treatment (assertive community treatment, individual or group social skills training, EDU in multiple family groups) | Standard treatment | 24M | **Transition,** psychotic, negative, disorganised symptoms | Integrated treatment (**Transition,**negative symptoms) | NR |
| (Albert et al. 2017)<br>High RoB | Mental Health Centre Copenhagen, Kildegaardsvej, Denmark | 6 Danish OPUS teams (5 in Copenhagen, and one in Aarhus) | ICD-10 (schizotypal disorder) | 83<br>39/44 | 26.6<br>18 to 35 | SB | Integrated treatment (family treatment, and skill training) | Treatment as usual | 6M | **Transition,** psychotic, negative, disorganised symptoms, substance use, functioning, employment status, cognitive function | None | OPUS Treatment (Negative symptoms, functioning)<br>Treatment as usual (Negative symptoms, functioning) |
| (Choi et al. 2017)<br>Some concerns | Institute of living in Hartford, CT, and COPE in New York State Psychiatric Institute, Columbia University, US | Mental health specialists | SIPS<br>SOPS | 62<br>31/31 | 18.35<br>16 to 24 | DB | Processing Speed Training (tablet-based cognitive training with pupillometric neurofeedback) | Placebo training | 2M | **Cognition (processing speed),**social functioning, depressive, anxiety symptoms | PST (**cognition**) | PST (**cognition**) |
| (Friedman-Yakoobian et al. 2022)<br>High RoB | NR | Social Media, online advertisements, clinicans, schools, universities | COPS<br>SIPS | 38<br>20/18 | 19.2 (Intervention)<br>19.1 (Control)<br>15 to 26 | SB | Cognition for Learning and for Understanding Everyday Social Situations (CLUES) | Enriched Acceptance and Commitment Therapy (EnACT) | 9M | **Social functioning,** psychotic symptoms, cognition | CLUES (social functioning, social cognition) | CLUES (social functioning, social cognition, positive symptoms, visual memory, reaction time)<br>EnACT (positive symptoms, visual memory, reaction time |

(*Continued*)

**Table 7.** Continued.

| Author, year/RCT/RoB | Centre | Referrals | CHR-P definition | N | Age | Blinding | Intervention | Control | Duration* | Primary and other outcomes | Superior treatment# | Improve from baseline within group |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (TD et al. 2018; Glenthøj et al. 2020; Kristensen et al. 2020; Glenthøj et al. 2021)<br>NCT02098408<br>High RoB | Mental Health Centre Copenhagen, Copenhagen, Denmark | Psychiatric in- and out-patient facilities of the catchment area of Copenhagen | CAARMS | 146<br>73/73 | 23.93 (Intervention)<br>23.90 (Control)<br>18 to 40 | SB | Cognitive remediation with treatment as usual | Treatment as usual | 6M | **Cognitive functioning,** clinical symptoms, social and role functioning, white matter organisation | None | NR |
| (Li H et al. 2021)<br>ChiCTR2000031741<br>High RoB | Shanghai Mental Health Centre, Suzhou Guangji Hospital | NR | SIPS<br>SOPS | 80<br>40/40 | 20.51<br>14 to 45 | SB | SMART (Specific Memory Attention Resource and Training) app | Treatment as usual | 3M | **Cognitive function** | SMART (**Attention/ vigilance**) | SMART (Attention/vigilance) |
| (Loewy et al. 2016)<br>NCT00655239<br>Some concerns | Psychiatry Department, San Francisco, US | Mental health specialists, primary care, general population (schools, internet) | SIPS | 83 | 18.2<br>12 to 30 | DB | Auditory training (AT) (laptop-based auditoy processing-based training) | Placebo training (computer gaming (CG) | 2M | **Cognition (verbal memory)**, positive, negative, disorganised symptoms, functioning | AT (**cognition,** disorganised symptoms) | AT (**cognition,** positive, negative, disorganised symptoms, functioning)<br>CG (positive, negative, disorganised symptoms, functioning) |
| (Miklowitz et al. 2014; Rinne et al. 2021)<br>NCT01907282<br>High RoB | NAPLS-2 consortium: Atlanta, Cambridge, Los Angeles, San Diego, Chapel Hill, New Haven, New York, US; Calgary, Canada | Health care providers, educators, social service agencies, general population (schools, internet)[108] | SIPS<br>SOPS | 129<br>66/63 | 17.4<br>12 to 32 | NR | Family-focused treatment for individuals at CHR | Family EDU (Enhanced care) | 6M | **Positive symptoms**, negative symptoms, functioning, family interaction, depression | Family-focused treatment (**Positive symptoms)** | Family focused therapy (**Positive symtoms,** negative symptoms, functioning)<br>Family EDU (Enhanced Care) (Neative symptoms, functioning) |
| (Reininghaus et al. 2019)<br>NTR4252<br>High RoB | INTERACT trial: 5 regions in Belgium and the Netherlands | Treating clinicians | CAARMS | 148<br>71/77 | 25<br>15 to 65 | SB | Acceptance and Commitment Therapy in Daily Life (ACT-DL) | Standard care | 12M | **Psychotic distress,** social functioning, symptom severity | ACT-DL (psychotic distress, negative symptoms, global functioning) | NR |
| (Piskulic et al. 2015)<br>Some concerns | At Risk for Mental Illness Research group Calgary, Canada | Health care providers, educators, social service agencies, general population (schools, internet) | SIPS | 32<br>18/14 | 19.72 (Intervention)<br>17.5 (Control)<br>14 to 35 | SB | Auditory processing CRT (Brain Fitness Program) | Placebo (video games) | 9M | **Cognition**, functioning, positive, negative symptoms, | None | Placebo (cognition)<br>CRT (cognition, functioning) |
| (Piskulic et al. 2018)<br>High RoB | At Risk for Mental Illness Research group, Calgary, Canada | Mental health agencies, school counselling services, community general population (outreach campaigns) | SOPS | 12<br>7/5 | 19.0 (Median, Intervention)<br>20.0 (Median, control)<br>14 to 25 | SB | CRT+ Motivational interviewing | CRT only | 2M | **Attrition rates** | NR | NR |
| (Tsai et al. 2021)<br>High RoB | China Medical University Hospital, Taiwan | NR | Chinese Version of Schizotypal Personality Questionnaire-Brief (CSPQ-B)<br>Chinese Mandarin State and Trait Anxiety Form- Y (CMSTAI-Y) | 92<br>46/46 | 21.34<br>20 to 35 | NR | Health-awareness-strengthening lifestyle program (HASL) | Waitlist control | 0.5M | Health promotion lifestyle, nutrition, physical exercise, quality of life, anxiety | HASL (health promotion lifestyle, nutrition, quality of life, anxiety) | HASL (self-actualization aspects of health promotion lifestyle, anxiety) |

(*Continued*)

## Table 7. Continued.

| Author, year/RCT/RoB | Centre | Referrals | CHR-P definition | N | Age | Blinding | Intervention | Control | Duration* | Primary and other outcomes | Superior treatment# | Improve from baseline within group |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (Zhao J et al. 2023)<br>ChiCTR2000039623<br>Low RoB | Beijing Anding Hospital, China | Referral from treating psychiatrists, Self-referral | SIPS | 57<br>28/29 | 25.5<br>18 to 35 | SB | EMDR | Waiting list | 3 M | **PTSD symptoms,**positive, anxiety, depressive symptoms, suicidal ideation | EMDR<br>(**PTSD symptoms**, positive, anxiety, depressive symptoms, suicidal ideation) | EMDR<br>(**PTSD symptoms**, positive, anxiety, depressive symptoms, suicidal ideation)<br>Waiting list<br>(**PTSD symptoms**, positive, anxiety, depressive symptoms, suicidal ideation) |
| **Biological interventions** | | | | | | | | | | | | |
| (Amminger et al. 2010; Mossaheb, Papageorgiou, et al. 2018; Mossaheb, Schäfer, et al. 2018)<br>NCT00396643<br>Low RoB | Psychosis detection unit, Vienna General Hospital, Austria | Mental health specialists, counsellors | PANSS, clinical interview accounting for CAARMS frequency criteria, and GRD definition | 81<br>41/40 | 16.4<br>13 to 25 | DB | ω − 3 PUFAs (1.2 grams daily)<br>+<br>NBI (9 sessions of pharmacological (AD, BDZ), psychological, psychosocial intervention including case-management with social support) | Placebo<br>+<br>NBI (9 sessions of pharmacological (AD, BDZ), psychological, psychosocial intervention including case-management with social support) | 3M | **Transition**, positive, negative, general, depressive symptoms, functioning, drop-out, lipid profile | ω − 3 PUFAs (**transition**, positive, negative, general symptoms, and functioning) | NR |
| (Cadenhead K et al. 2017; Cadenhead KS et al. 2019)<br>NCT01429454<br>Low RoB | NAPLS Consortium | Mental health specialists, schools, colleges primary care | SIPS | 127 | 18.69<br>12-30 | DB | ω − 3 PUFAs (700 mg EPA, 480 mg DHA) | Placebo | 6M | **Transition**, cardiometabolic, dietary Omega 3 fatty acids and oxidative stress indices | None | ω − 3 PUFAs (positive, functioning) |
| (Davies et al. 2023; Davies C. et al. 2024)<br>ISRCTN46322781<br>High RoB | Institute of Psychiatry, Psychology and Neuroscience, King's College, London, UK | NR | CAARMS | 52<br>33/<br>19 | 22.7<br>23.9 /24.1<br>18 to 35 | DB | Single oral dose of 600 mg of Cannabidiol (CBD) | Placebo | 0.03M (one day) | **Hippocampal blood flow**[49]<br>**Hippocampal glutamate**[48] | Single oral dose of 600 mg of Cannabidiol (CBD)<br>**(hippocampal blood flow, hippocampal glutamate)** | NP |
| (Davies Cathy et al. 2024)<br>ISRCTN48799530<br>Some concerns | Outreach and support in South-London (OASIS) service, London, UK; Maudsley NHS Foundation Trust, London, UK | NR | CAARMS | 50<br>33/<br>17 | 23.2<br>24.2<br>18 to 35 | DB | 40IU intranasal oxytocin (two parallel [CHRP vs healthy controls] crossover design) | Placebo (two parallel [CHRP vs healthy controls] crossover design) | 0.07M (2 days) | **Functional brain network topology,**(including network organisation in subcortical and cortical regions) | 40IU intranasal oxytocin **(functional brain network topology**) | NP |
| (Bhattacharyya et al. 2018; Appiah-Kusi et al. 2020; Davies, Wilson, et al. 2020)<br>ISRCTN46322781<br>Low RoB | King's College, London IoPPN, UK | Early intervention service | CAARMS | 52<br>16/17 | 22.43<br>NA | DB | Cannabidiol (600 mg) | Placebo[§] | 0 | **fMRI BOLD signal during encoding, recall and recall**endocannabinoid, cortisol, activity of the medial temporal lobe and striatum during fear processing | Cannabidiol (**encoding, recall**) | NP |
| (Wilson et al. 2019)<br>Low RoB | Kings College London, London UK Clinical Research Facility | Early intervention service | CAARMS | 33 | NR<br>18 to 35 | DB | Cannabidiol (600 mg) | Placebo, Healthy Control (Not CHR, no CBD administered) | NA (cross-sectional) | **Behavioural performance (5 domains: mean monetary reward, accuracy, reaction time, false-starts, any trial responses)** | CHR-CBD (Reaction time, false starts) | NP |
| (Davies, Paloyelis, et al. 2019; Davies, Rutigliano, et al. 2019; Schmidt A et al. 2020)<br>Low RoB | NR | Two early detection services: The OASIS and Tower Hamlets Early Detection Service | CAARMS | 30 | NR<br>18 to 35 | DB | Intranasal oxytocin (40IU) | Placebo | 0 | **Global cerebral blood flow,**hippocampal cerebral blood flow, choline in ACC, cognitive and social empathy | Intranasal oxytocin (hippocampal cerebral blood flow) | NP |

(*Continued*)

## Table 7. Continued.

| Author, year/RCT/RoB | Centre | Referrals | CHR-P definition | N | Age | Blinding | Intervention | Control | Duration* | Primary and other outcomes | Superior treatment# | Improve from baseline within group |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (Kantrowitz et al. 2015)<br>NCT00826202<br>Low RoB | Nathan Kline Institute, Yale, Zucker Hillside Hospital, and New York State Psychiatry Institute, US | Mental health specialists, primary care | SOPS | 44<br>20/24 | 19.5<br>13 to 35 | DB | D-serine | Placebo | 4M | **Negative symptoms**, positive symptoms, cognition, sleep | D-serine (**negative symptoms**) | D-serine (**negative symptoms**) |
| (Livingston et al. 2024)<br>NCT06190483<br>Low RoB | Outreach and Support in South London (OASIS), South London and Maudsley NHS Foundation Trust | NR | CAARMS | 66<br>24/<br>22 | 25.3<br>18 to 32 | DB | 5 mg of oral diazepam (crossover design) | Placebo (crossover design) | 0.5M | **Hippocampal regional cerebral blood flow (rCBF)** | Diazepam **(Hippocampal regional cerebral blood flow [rCBF])** | NP |
| (Qurashi et al. 2024)<br>NCT02569307<br>Low RoB | Abasi Shaheed Hospital, Karachi Pakistan; Civil hospital Karachi, Karachi, Pakistan; Karwn e Hayat, Karachi Pakistan; Colleges and Universities, Karchi Pakistan; General Practitioners, Karachi Pakistan; Institute of Behavioural Sciences, Karachi Pakistan | Self-referrals | CAARMS | 326<br>82/<br>82/<br>82/<br>80 | 24<br>16 to 25 | DB | 1. Minocycline<br>2. omega-3 fatty acids<br>3. minocycline + omega-3 fatty acids | Double placebo | 6M | **Transition to psychosis,**positive, depressive symptoms, social and role functioning | None | omega-3 fatty acids (positive, depressive symptoms [among non-transitioners])<br>minocycline + omega-3 fatty acids (positive, depressive symptoms [among non-transitioners]) |
| (McGlashan et al. 2006)<br>Low RoB | PRIME clinics: Yale, North Carolina/ Chapel Hill, US; Calgary, Toronto, Canada. | Clinicians, general population (advertisements) | SIPS | 60<br>31/29 | 17.7<br>12 to 45 | DB | Olanzapine (5–15mg) | Placebo | 12M | **Transition**, positive, negative, general, depressive, manic symptoms, functioning, drop-out | None | Olanzapine (total, positive symptoms, functioning)<br>Placebo (functioning) |
| (Ruhrmann et al. 2007)<br>High RoB | Departments of Psychiatry, Cologne, Bonn, Dusseldorf, Munich, Germany | Psychologists, psychiatrists, general practitioners, school or university counselling services, self-referrals | ERIaos<br>ERI-BAPPSS | 124<br>65/59 | 25.6<br>18–36 | OL | Needs-focused intervention + amisulpride (50–800 mg/day) | Needs-focused intervention only | 24M | **Positive symptoms**, negative, depressive, basic symptoms, functioning | Needs-focused intervention + amisulpride (positive symptoms, negative symptoms, basic symptoms, functioning**)** | Needs-focused intervention + amisulpride (**positive symptoms**, negative symptoms, functioning, depressive symptoms)<br>Needs-focused intervention only (depressive symptoms) |
| (Tang et al. 2023)<br>ChiCTR-INR-16009566<br>High RoB | Shanghai Mental Health Centre, China | Shanghai At-Risk for Psychosis Program (SHARP) | SIPS<br>SOPS | 65<br>31/<br>27 | 19<br>15 to 45 | DB | TMS | Sham TMS | 0.5M | **Visual spatial learning (VSL),**cognitive functioning, transition to psychosis at 12 M | TMS (**VSL performance**, transition to psychosis at 12M) | TMS (**VSL performance and precision**) |
| (Woods SW et al. 2013)<br>NTC0026874<br>NTCT00291226<br>Low RoB | PRIME Research Clinic, Yale University, New Haven, USA | Community education efforts | COPS<br>SOPS | 8<br>4/4 | 15.3 (Intervention)<br>16.5 (Control)<br>15 to 17 | DB | Glycine (0.8 g/kg/d) | Placebo | 3M | **SOPS total score, positive, negative, disorganisation, general symptoms,** depressive symptom severity, cognition | Glycine (Depressive symptoms) | Glycine (**SOPS total, positive, negative, disorganisation, general symptoms,** depressive symptoms**)** |

(*Continued*)

## Table 7. Continued.

| Author, year/RCT/RoB | Centre | Referrals | CHR-P definition | N | Age | Blinding | Intervention | Control | Duration* | Primary and other outcomes | Superior treatment# | Improve from baseline within group |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (Woods S et al. 2017)<br>Low RoB | Atlanta, Los Angeles, San Diego, San Francisco, Glen Oakes, Detroit, Worcester, Boston,, New Haven, Chapel Hill, US; Calgary, Canada | Clinician referral | SIPS<br>SOPS | 51<br>24/27 | 22.3<br>16 to 40 | DB | Ziprasidone (20–160mg/d) | Placebo | 6M | **Transition,** positive symptoms | Ziprasidone<br>(Positive symptoms) | NR |
| (Zhu H et al. 2023)<br>ChiCTR-IOR-17013513<br>High RoB | Beijing Anding Hospital, China | NR | SIPS | 80<br>37/<br>40 | 19.76<br>16 to 30 | DB | Shi-Zhen-An-Shen Herbal Formula Granule (SZAS-HFG) + placebo for aripiprazole | Aripiprazole + placebo for SZAS-HFG | 3M | **Positive symptoms, cognitive functioning,**general functioning | Shi-Zhen-An-Shen Herbal Formula Granule (SZAS-HFG) + placebo for aripiprazole<br>(general functioning) | NR |
| **Combined (psychosocial plus pharmacological) interventions** | | | | | | | | | | | | |
| (Bechdolf et al. 2011; 2017; 2023)<br>osf = 631fa13b1e f84d7686bf185 e6d89de17<br>Some concerns | 6 sites in Germany (University of Cologne; Rheinische Friedrich-Wilhelm University; Heinrich-Heine University; Ludwig-Maximilian-Universität,; Charite-Universitätsmedizin, Berlin; Campus Charite- Mitte, Berlin; University of Göttingen,; University of Aachen) | Mental health professionals or self-referrals | SIPS<br>SOPS<br>SPIA | 280<br>129/<br>96/<br>55 | 24.4<br>18 to 49 | DB aripiprazole<br>SB CBT | 1.CBT<br>2. Aripiprazole+clinical management | Placebo<br>+<br>Clinical management | 12 M | **Transition to psychosis,** time to transition, psychopathological symptoms, psychosocial functioning, safety, side effects | None | All arms (Positive and disorganisation symptoms, basic symptoms [COGDIS], psychosocial functioning, and depression) |
| (McGorry et al. 2002)<br>High RoB | PACE clinic, Melbourne, Australia | Mental health specialists, primary care, general population (schools) | CAARMS | 59<br>31/28 | 20<br>14 to 30 | SB | Specific Prevention Intervention<br>(NBI<br>+<br>risperidone [1–2mg]<br>+<br>CBT[126]) | NBI (pharmacological (AD, BDZ), psychological, psychosocial interventions including case-management with social support) | 6M | **Transition** | SPI (**transition**) | NR |
| (Yung et al. 2011; McGorry et al. 2013)<br>ACTRN01260 5000247673<br>Low RoB | PACE Clinic, Melbourne, Australia | NR | CAARMS | 115<br>43/44/28 | 18.1<br>14–30 | DB | Risperidone (0.5–2 mg/day) + CBT | CBT + placebo, supportive therapy + placebo | 12M | **Transition,** psychiatric symptoms, psychosocial functioning, quality of life | None | Risperidone (0.5–2 mg/day) + CBT (negative symptoms, psychosocial functioning)<br>CBT+Placebo (negative symptoms, psychosocial functioning)<br>Supportive therapy+Placebo (negative symptoms, psychosocial functioning) |

(*Continued*)

## Table 7. Continued.

| Author, year/RCT/RoB | Centre | Referrals | CHR-P definition | N | Age | Blinding | Intervention | Control | Duration* | Primary and other outcomes | Superior treatment# | Improve from baseline within group |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (McGorry et al. 2017; Nelson et al. 2018; Berger et al. 2019; Bolt et al. 2019; Alqarni et al. 2020; Amminger et al. 2020; Mallawaarachchi et al. 2020)<br>12608000475347<br>Low RoB | Melbourne, Sidney, Australia; Vienna, Austria; Copenhagen, Denmark; Hong Kong; Jena, Germany; Amsterdam, Netherlands; Singapore; Basel, Zurich, Switzerland; | Mental health specialists | CAARMS | 304<br>153/151 | 19.1<br>13 to 40 | DB | ω − 3 PUFAs (1.4 grams daily)<br>+<br>CBCM | Placebo<br>+<br>CBCM | 6M | **Transition**, total, negative, depressive, manic symptoms, functioning, erythrocyte lipid species | Placebo (functioning) | NR |
| (McGorry et al. 2023)<br>NCT02751632<br>Low RoB | Personal Assessment and Crisis Evaluation (PACE) clinic; 4 headspace centres | NR | CAARMS | 342<br>Step 1: 342<br>Step 2: 281<br>Step 3: 138 | 12 to 25 | DB | Multiple assignment randomised trial (SMART) consisting of three steps:<br>Step 1: Support and problem solving (SPS) (1.5 months);<br>Step 2: SPS vs CBCM (4.5 months);<br>Step 3: CBCM + Antidepressant Medication vs CBCM + Placebo (6 months) | Monitoring | 12M | **Social and role functioning,** general psychopathology, negative, depressive, positive symptoms, quality of life, cognitive biases | None | NR |
| (Wasserthal et al. 2024)<br>NCT03149107<br>Low RoB | 11 sites in Germany (University Hospital of Bonn; University Hospital of Cologne; University of Oldenburg; University of Heidelberg; University of Regensburg; RWTH Aachen University; Charité Universitätsmedizin; Ludwig Maximilian University of Munich; University of Tübingen; Vivantes Klinikum Am Urban; LVR-Clinic Bonn) | Self-referred in early detection facilities, health care providers | SIPS<br>SPI-A | 48<br>23/24 | 24.9<br>15 to 45 | DB<br>SB | 1. N-acetylcysteine (NAC)<br>2. Integrated Preventive Psychological Intervention (IPPI) | 1. Placebo (PLC) for NAC<br>2. Psychological Stress Management (PSM) for IPPI | 6.5M | **Transition to psychosis,**social functioning, social cognition, neurocognitive capabilities | None | None |

*Legend.* AD: antidepressants; BDZ: benzodiazepines; BPRS: Brief Psychiatric Rating Scale; CAARMS: Comprehensive Assessment of At-Risk Mental State; CAMH: Centre for Addiction and Mental Health; CBCM: Cognitive Behavioural Case Management; CBT: cognitive behavioural therapy; COPE: Centre of Prevention and Evaluation; (C)CRT: computerised cognitive-remediation therapy; DB: double-blind; EMDR: eye movement desensitisation and reprocessing; EDU: psychoeducation; ERIraos: Early Recognition Inventory; ERI-BAPPSS: Early Recognition Inventory, Basic and Positive Psychotic Spectrum Symptoms score; GRD: Genetic risk and Deterioration Syndrome; IRAOS: Retrospective Assessment of the Onset of Schizophrenia; M: months; NBI: needs-based interventions; NP: not pertinent; OL: open label; PACE: Personal Assessment and Crisis Evaluation; PANSS: Positive And Negative Symptoms Scale; PRIME: Prevention Through Risk Identification, Management, and Education; PUFAs: polyunsaturated fatty acids; PTSD: post-traumatic stress disorder; RoB: risk of bias; SB: single-blind; SIPS: Structured Interview for Prodromal Symptoms; SOPS: Scale Of Prodromal Symptoms; SPIA: Schizophrenia Proneness Instrument, Adult version; ST: skills training; T: time points; TMS: transcranial magnetic stimulation; W: weeks;* : duration of randomised treatments: rounded to months; #: only outcomes where the intervention was statistically significantly superior to control were considered; §: also included healthy control group, not reported as not pertinent. Edited from (McGorry et al. 2002; Morrison et al. 2004; McGlashan et al. 2006; Nordentoft et al. 2006; Morrison et al. 2007; Ruhrmann et al. 2007; Amminger et al. 2010; Addington et al. 2011; Bechdolf et al. 2011; Yung et al. 2011; Bechdolf et al. 2012; Morrison et al. 2012; van der Gaag et al. 2012; McGorry et al. 2013; Woods SW et al. 2013; Miklowitz et al. 2014; Kantrowitz et al. 2015; Piskulic et al. 2015; Ising et al. 2016; Loewy et al. 2016; Stain et al. 2016; Albert et al. 2017; Bechdolf et al. 2017; Cadenhead K et al. 2017; Choi et al. 2017; McGorry et al. 2017; Woods S et al. 2017; Bhattacharyya et al. 2018; Mossaheb, Papageorgiou, et al. 2018; Mossaheb, Schäfer, et al. 2018; Nelson et al. 2018; Piskulic et al. 2018; TD et al. 2018; Berger et al. 2019; Bolt et al. 2019; Cadenhead KS et al. 2019; Davies, Paloyelis, et al. 2019; Davies, Rutigliano, et al. 2019; Pozza et al. 2019; Wessels et al. 2019; Wilson et al. 2019; Alqarni et al. 2020; Amminger et al. 2020; Appiah-Kusi et al. 2020; Davies, Wilson, et al. 2020; Glenthøj et al. 2020; Kristensen et al. 2020; Mallawaarachchi et al. 2020; Schmidt A et al. 2020; Glenthøj et al. 2021; Li H et al. 2021; Myin-Germeys et al. 2021; Pozza et al. 2021; Rinne et al. 2021; Tsai et al. 2021; Friedman-Yakoobian et al. 2022; Addington, Liu, et al. 2023; Bechdolf et al. 2023; Davies et al. 2023; McGorry et al. 2023; Tang et al. 2023; Waite et al. 2023; Zhao J et al. 2023; Zhu H et al. 2023; Davies, Bossong et al. 2024; Davies, Martins et al. 2024; Livingston et al. 2024; Qurashi et al. 2024; Wasserthal et al. 2024).

Bechdolf et al. 2023; McGorry et al. 2023; Wasserthal et al. 2024). The results are descriptively reported in Table 7 for both primary and secondary outcomes. Eight RCTs compared CBT with a control intervention, focusing on transition to psychosis as an outcome in six (Morrison et al. 2004; 2007; Addington et al. 2011; Morrison et al. 2012; van der Gaag et al. 2012; Ising et al. 2016; Stain et al. 2016; Pozza et al. 2019, 2021) of these. In only three (Morrison et al. 2004; 2007; van der Gaag et al. 2012; Ising et al. 2016; Pozza et al. 2019, 2021) of these six RCTs CBT outperformed the control group in reducing the transition rate. Of the 14 RCTs on other psychosocial interventions, only integrated psychological intervention outperformed the control group in two RCTs regarding transition to psychosis (Nordentoft et al. 2006; Bechdolf et al. 2012; Wessels et al. 2019), and one more recent RCT found no superiority for this intervention (Albert et al. 2017). Of the RCTs testing biological and combined interventions, ω-3 PUFAs outperformed placebo on transition in one RCT (Amminger et al. 2010; Mossaheb, Papageorgiou, et al. 2018; Mossaheb, Schäfer, et al. 2018), but no difference emerged in three subsequent RCTs (Cadenhead K et al. 2017; McGorry et al. 2017; Nelson et al. 2018; Berger et al. 2019; Bolt et al. 2019; Cadenhead KS et al. 2019; Alqarni et al. 2020; Amminger et al. 2020; Mallawaarachchi et al. 2020; Qurashi et al. 2024). Of the five RCTs testing combined interventions, needs-based interventions plus low-dose risperidone and CBT outperformed needs-based intervention alone on transition in an earlier RCT (McGorry et al. 2002); however, four more recent RCTs found no superiority for any combined intervention over control conditions (Bechdolf et al. 2011; Yung et al. 2011; McGorry et al. 2013; Bechdolf et al. 2017; McGorry et al. 2017; Nelson et al. 2018; Berger et al. 2019; Bolt et al. 2019; Alqarni et al. 2020; Amminger et al. 2020; Mallawaarachchi et al. 2020; Bechdolf et al. 2023; McGorry et al. 2023; Wasserthal et al. 2024). No other psychosocial or biological or combined interventions was superior to other interventions on transition to psychosis in CHR-P subjects.

### *3.1.7. Meta-analyses and network meta-analyses of randomised controlled trials*

The study selection flow of the umbrella review of (network) meta-analyses of RCTs in subjects meeting CHR-P status criteria, is reported in eFigure 7 (Table 8). Out of initial 350 hits, we ultimately included 11 (network) meta-analyses (Preti and Cella 2010; Stafford et al. 2013; van der Gaag et al. 2013; Hutton and Taylor 2014; Davies, Cipriani, et al. 2018; Davies, Radua, et al. 2018; Bosnjak Kuharic et al. 2019; Fusar-Poli, Radua, et al. 2021; Mei et al. 2021; Fusar-Poli, Radua, et al. 2022; Zheng et al. 2022). Studies excluded after full-text assessment, with reason for exclusion, are reported in eTable 9.

Details on outcomes, sample size, interventions, and results of included (network) meta-analyses are reported in Table 8.

Out of 11 publications, nine only conducted pairwise meta-analyses (Preti and Cella 2010; Stafford et al. 2013; van der Gaag et al. 2013; Hutton and Taylor 2014; Bosnjak Kuharic et al. 2019; Fusar-Poli, Radua, et al. 2021; Mei et al. 2021; Fusar-Poli, Radua, et al. 2022; Zheng et al. 2022), and two conducted a network meta-analysis (Davies, Cipriani, et al. 2018; Davies, Radua, et al. 2018). All (network) meta-analyses considered a mix of psychosocial and pharmacological interventions.

Among the two network meta-analyses, as primary outcomes, one considered psychotic symptoms (Davies, Radua, et al. 2018), and one considered transition to psychosis (Davies, Cipriani, et al. 2018). No significant result emerged for transition to psychosis. Ziprasidone as augmentation of needs-based intervention (NBI) outperformed family CBT with/without risperidone in one network meta-analysis (Davies, Radua, et al. 2018) regarding attenuated psychotic symptoms.

Regarding transition to psychosis, in pairwise meta-analyses, all interventions pooled together outperformed TAU in three meta-analyses (Preti and Cella 2010; van der Gaag et al. 2013; Mei et al. 2021). Antipsychotics outperformed TAU in one meta-analysis (van der Gaag et al. 2013). CBT outperformed supportive therapy in one meta-analysis (Stafford et al. 2013), and CBT plus supportive therapy outperformed supportive therapy alone in one meta-analysis (Bosnjak Kuharic et al. 2019). CBT-informed treatment outperformed other treatments in three meta-analyses (Hutton and Taylor 2014; Mei et al. 2021; Zheng et al. 2022). Importantly, significant results regarding CBT on transition to psychosis were not confirmed in any network meta-analysis (see above), nor in two additional meta-analyses (Fusar-Poli, Radua, et al. 2021; 2022). Regarding other outcomes, CBT also outperformed supportive therapy on psychotic symptoms in one meta-analysis (Hutton and Taylor 2014). No difference emerged from other outcomes (Hutton and Taylor 2014; Mei et al. 2021; Zheng et al. 2022). Differences in the included studies across eligible meta-analyses might explain (part of) the differences in results, are described in Table 8.

**Table 8.** Network and pairwise meta-analyses on randomised controlled trials aiming to prevent psychosis in people at clinical high risk of psychosis (expanded from (Fusar-Poli, Davies, et al. 2019)).

| Author, year | Source | Primary outcome, other outcomes | RCT-N | Interventions | Significant findings of primary analyses, random-effects model |
|---|---|---|---|---|---|
| (Preti and Cella 2010) | MA | Transition | 5-180 | CBT, CBT+RIS, IPI, monitoring, NBI, OLA, Om3, Pbo, TAU | Transition: all interventions pooled together<br>No other significant findings |
| (Stafford et al. 2013) | MA | Transition | 11-1,246 | CBT, CBT+Pbo, CBT+RIS, CBT+SUP, IPI, NBI, NBI+AMI, OLA, Om3, Pbo, SUP, SUP+Pbo, TAU | Transition: i) CBT > SUP at 6–12 months (RR = 0.54, 95%CI = 0.34–0.86), 12+ months (RR = 0.63, 95%CI = 0.40–0.99), ii) CBT+RIS > SUP at 6 months (RR = 0.35, 95%CI = 0.13–0.95)<br>No other significant findings |
| (van der Gaag et al. 2013) | MA | Transition | 10-NA | CBT, CBT+RIS, OLA, IPI, Pbo, TAU, antipsychotics | Transition: i) all interventions pooled together, ii) Antipsychotics (RR = 0.55, 95%CI = NA, $p = 0.029$).<br>No other significant findings |
| (Hutton and Taylor 2014) | MA | Transition, APS, functioning, distress, QoL | 6-800 | CBT, CBT+monitoring, CBT+Pbo, CBT+RIS, IPI, monitoring, SUP, SUP+Pbo | Transition: CBT-informed > others at 12 months (RR = 0.45, 95%CI = 0.28–0.73), at 18–24 months (RR = 0.41, 95%CI = 0.23–0.72).<br>APS: CBT-informed > others at 12 months (g = −0.25, 95%CI −0.46to − 0.03)<br>No other significant findings |
| (Davies, Cipriani, et al. 2018) | NMA | Transition, acceptability | 16-2,035 | NBI, CBT-F + RIS+NBI, CBT-F + NBI, CBT-F + CBT-V + NBI, Dser + NBI, IPI, FFT+NBI, OLA+NBI, Om3 + NBI, ZIP+NBI | No significant findings |
| (Davies, Radua, et al. 2018) | NMA | APS, acceptability | 14-1,707 | NBI, ARI+NBI, CBT-F + NBI, CBT-F + RIS+NBI, Dser + NBI, FFT+NBI, IPI, OLA+NBI, Om3 + NBI, ZIP+NBI | APS: i) ZIP+NBI > NBI (SMD = −1.10, 95%CI = −2.04to − 0.15), >CBT-F (SMD = −1.03, 95%CI = −2.05to − 0.01), >CBT-F + RIS+NBI (SMD = −1.18, 95%CI −2.29to − 0.07) at 6 months.<br>Acceptability: NBI+ARI > NBI+OLA (OR = 3.73, 95%CI = 1.01–13.81)<br>No other significant findings |
| (Bosnjak Kuharic et al. 2019) | MA | Transition | 20-2,151 | NBI, Pbo, SUP, aminoacids, AMI+NBI, CBT, CBT + NBI + RIS, CBT + Pbo, CBT + RIS, CBT + SUP, CT, EC, FT, IPI, OLA + SUP, Om3, SUP, SUP + Pbo, TAU | Transition: CBT+SUP > SUP, transition 18 months (RR = 0.45, 95%CI = 0.23–0.89)[+]<br>No other significant findings |
| (Mei et al. 2021)[#] | MA | Transition, APS, negative symptoms, depressive symptoms, anxiety symptoms, distress, QoL, functioning | 26-2,351 | CBD, CBCM+Pbo, CBT, CBT+monitoring, CBT+RIS, CBT+TAU, COMP, CRT, CRT+TAU, Dser, EC, FFT, FT, Gly, IPI, monitoring, NBI, NDRL+TAU, OLA+SUP, Om3, Om3 + CBCM, Pbo, SUP, SUP+Pbo, TAU, ZIP | Transition: All interventions pooled together<br>CBT > others at EoT (RR = 0.55, 95%CI = 0.31–0.99), 12 months (RR = 0.52, 95%CI = 0.33–0.82), 18+ months (RR = 0.60, 95%CI = 0.42–0.84)[#]<br>APS: All interventions pooled together<br>No other significant findings |
| (Fusar-Poli, Radua, et al. 2021)[##] | MA | Transition | 7-NA | CBT, CBT+monitoring, CBT+Pbo, CBT+TAU, monitoring, NDRL+TAU, SUP, SUP+Pbo, TAU | No significant findings [##] |
| (Zheng et al. 2022)* | MA | Transition, APS, depressive symptoms, distress, functioning, QoL | 10-1,128 | CBT, CBT+RIS, CBT+NBI, NBI | Transition: CBT > NBI 6–12 (RR = 0.44, 95%CI = 0.30–0.64), 12–24 (RR = 0.46, 95%CI = 0.30–0.69), 24+ (RR = 0.58, 0.35–0.95) months<br>No other significant findings |
| (Fusar-Poli, Radua, et al. 2022)[###] | MA | Transition | 9-NA | CBT, CBT+RIS, CBT+NBI, NBI | No significant findings[###] |

*Legend*. Acceptability: all-cause discontinuation; AMI: amisulpride; APS: attenuated psychotic symptoms; ARI: aripiprazole; CBCM: CBCM,cognitive-behavioural case management; CBT: cognitive behavioural therapy; CBT-F: French & Morrison CBT protocol; CBT-V: van der Gaag CBT protocol; CI: confidence interval; COMP: computer games; CT: cognitive training; Dser: D-serine; EC: enhanced care; FFT: family-focused therapy; FT: family treatment; Gly: glycine; IPI: integrated psychological interventions; MA: meta-analysis; NBI: needs-based interventions (including placebo); NDRL: non directive reflective listening; NMA: network meta-analysis; OLA: olanzapine; Om3: omega-3 fatty acids; Pbo: placebo; QoL: quality of life; RCT: randomised controlled trial; RIS: risperidone; RR: risk ratio; SUP: supportive; TAU: treatment as usual; Total RCT/n: overall number of RCTs and subjects included in the meta-analysis or network meta-analysis across any outcome; ZIP: ziprasidone. Bold outcome was primary outcome of review; [+]: GRADE = very low; [#]: excluding PREVENT, and including RCT with high risk of bias; [##]: excluding RCT with high risk of bias, and including PREVENT trial; [###]: excluding RCT with high risk of bias, one Chinese RCT with high risk of bias, and including PREVENT trial; *: excluding PREVENT, including three RCTs with high risk of bias. Edited from (Preti and Cella 2010; Stafford et al. 2013; van der Gaag et al. 2013; Hutton and Taylor 2014; Schmidt SJ et al. 2015; Davies, Cipriani, et al. 2018; Davies, Radua, et al. 2018; Devoe et al. 2018; Bosnjak Kuharic et al. 2019; Devoe et al. 2019b, 2019a, 2020; Fusar-Poli, Radua, et al. 2021; Mei et al. 2021; Fusar-Poli, Radua, et al. 2022; Zheng et al. 2022).

### 3.1.8. Studies comparing psychosis prevention services with other services, and cost-effectiveness of psychosis prevention services

We updated a systematic review (Sizer et al. 2022) on studies comparing psychosis prevention services with other services (Table 9). The study selection flow of the update of that systematic review is reported in eFigure 8. Studies excluded after full-text assessment, with reason for exclusion, are reported in eTable 10. Three cohort studies were reported in the original systematic review (Sizer et al. 2022), comparing 78 subjects with FEP after meeting CHR-P criteria in prevention services (CHR-P-T) versus 253 subjects not being assessed in psychosis prevention services and directly presenting with FEP (FEP-D) (Table 9). One study set in Taiwan showed no difference on cognitive

**Table 9.** Studies comparing psychosis prevention services with other services, and cost-effectiveness of psychosis prevention services.

| Author, year<br>Country | N<br>Months | Design<br>Model<br>Intervention/service | Outcomes | Findings |
|---|---|---|---|---|
| **Psychosis prevention service-focused studies** (Sizer et al. 2022) | | | | |
| (Yoviene Sykes et al. 2020)<br>US | 97<br>12M | Cohort<br>Mean or frequency comparisons<br>FEP seen in UHR service vs FEP not seen | Any hospitalisation, number of hospitalisations, length of stay, any emergency room visit, repeat diagnosis of psychosis or continued antipsychotic prescription, DUP | UHR service superior in DUP<br>UHR had more emergency visits.<br>No difference in any hospitalisation, number of hospitalisations, length of hospital stay, repeat diagnosis of psychosis. |
| (Valmaggia et al. 2015)<br>UK | 190<br>12M | Cohort<br>Mean or frequency comparisons<br>FEP seen in UHR service vs FEP not seen | Any hospitalisation, total involuntary admissions, length of hospital stay, DUP | UHR service superior on any hospitalisation, involuntary admissions, DUP.<br>No difference in length of hospital stay |
| (Liu et al. 2015)<br>Taiwan | 67<br>12M | Cohort<br>Mean or frequency comparisons<br>FEP seen in UHR service vs FEP not seen | WCST, WAIS-III, TMT, verbal fluency test, Weschler Memory test | No difference in any cognitive function |
| (Fusar-Poli P. et al. 2020) | 1561<br>24M | Cohort<br>Mean or frequency comparisons<br>FEP seen in UHR service vs FEP not seen | Treatment with antipsychotic, informal hospitalisation, compulsory hospitalisation, treatment with clozapine, and length in hospital stay | UHR service inferior in antipsychotic medication (at 3, 6, and 24 months, not 12 months), informal and involuntary hospital admission (at all time points), and length in hospital stay (at all time points).<br>No difference in clozapine |
| **Cost-effectiveness** | | | | |
| (Ising et al. 2015)<br>NL | 196<br>18M | RCT<br>Incremental cost-effectiveness ratio with nonparametric bootstrapping<br>TAU + CBT vs TAU | Transition, QALY.<br>Intervention, medical, travel, loss of productivity costs. | Cost-effectiveness: CBT avoided 89.5% v. 76.2% transition to psychosis, lower cost by US$844 (£551) per prevented psychosis, 63.7% probability of being more cost effective.<br>Cost-utility: CBT had similar QALY 0.60 v. 0.57, 52.3% probability of being the superior treatment. |
| (Ising et al. 2017)<br>NL | 196<br>48M | RCT<br>Incremental cost-effectiveness ratio with nonparametric bootstrapping<br>TAU + CBT vs TAU | Transition, QALY.<br>Intervention, medical, travel, loss of productivity costs. | Cost-effectiveness: CBT avoided transition to psychosis (with a risk difference of 0.122; $b = 1.324$, SEb = 0.017, $z = 7.99$, $p < 0.001$), lower cost by US$ 577 per participant, 83% probability of being more cost effective.<br>Cost-utility: CBT had similar QALY 2.63 vs 2.46, 75% probability of being superior treatment, and 92% probability of being cost-effective at €20 000 threshold per QALY. |
| (Ologundudu et al. 2023)<br>CA | 1000<br>15 year | Cohort (simulated)<br>Decision modelling, Markov model<br>Standard treat all CHR-P strategy vs Risk stratification treatment strategy (i.e. CHR-P with ≥20 % risk of transition only) | Transition, QALY. | Treating only CHR-P individuals with a risk of ≥20% resulted in lower costs ($1,398) and fewer quality-adjusted life-years (0.055 QALYs) per person compared to a strategy of treating every CHR-P individual. The incremental cost-effectiveness ratio (ICER) for the 'treat all' approach was $25,448 per QALY, indicating that treating all individuals may be a cost-effective strategy. |

(*Continued*)

**Table 9.** Continued.

| Author, year<br>Country | N<br>Months | Design<br>Model<br>Intervention/service | Outcomes | Findings |
|---|---|---|---|---|
| (Phillips et al. 2009)<br>AU | 59<br>36M | RCT<br>Mean costs comparison<br>SPI vs NBI | Transition to psychosis.<br>Outpatient, pharmacological, inpatient costs. | Lower transition to psychosis, but no difference in costs |
| (Perez et al. 2015)<br>UK | 104 centres<br>24M | Cluster RCT<br>Decision analytic modelling<br>Primary care practices (clusters) assigned to:<br>i) 2 year low-intensity intervention, guidelines, postal campaign; ii) high-intensity intervention, liaising mental health professional; iii) practice as usual | Number of referrals, true positive referral (UHR or FEP).<br>Incremental cost per additional true positive identified | Total cost per true-positive referral in the 2 year follow-up was £26 785 in high-intensity practices, £27 840 in low-intensity practices, and £30 007 in PAU practices. The high-intensive intervention, which improved liaison between primary and secondary care for people presenting early signs of psychosis, was found to be both clinically and cost effective. |
| (Valmaggia et al. 2009)<br>UK | 114<br>24M | Cohort<br>Decision modelling<br>Psychosis prevention service (OASIS) vs early intervention service | Services use and pharmacological treatment following referral and employment | Over the initial 12 months from presentation, the costs of the OASIS intervention were £1872 higher than TAU. However, after 24 months they were £961 less than TAU. |
| (Wijnen et al. 2020)<br>NL | 2,514<br>120M | Cohort (simulated)<br>PsyMod, Markov model<br>CBT vs care as usual | Service use, treatment and utilities | CBTuhr resulted in a per-patient increase of 0.06 QALYs and a per patient cost reduction of €654 (dominant incremental cost-effectiveness ratio) with a reduction in 5-year healthcare costs of €1,002,166. |
| (Campion et al. 2019)<br>UK | 857/year<br>120 M | Cohort (model)<br>Knapp model<br>Psychosis prevention service (OASIS) vs standard care | National health service costs, productivity costs | Reach all new CHR-P cases each year would need extra costs of £1 904 396 in first year (from increased service costs), but free up resources of £19.7 m over 10 years with an estimated 10-year cost of implementation gap for each 1 year cohort of £18.9 m |
| (Brimblecombe et al. 2017)<br>UK | 20<br>36M | Cohort<br>Pre vs post<br>Psychosis prevention service, within-subject pre-post comparison | Service use, crime, employment costs | Mental health improved or stayed the same, employment rates improved, total cost difference of £621 425 |
| (Jin et al. 2021)<br>UK | 200,000<br>Lifetime | Cohort (simulated)<br>Cost-utility analysis, discrete-event simulation<br>CBT UHR 100% vs 41.01% | Lifetime costs, QALY | Cost-effective above willingness-to-pay £20 000 and £30 000 threshold per QALY |
| (Jin et al. 2020)<br>UK | 69,800<br>Lifetime | Cohort (simulated)<br>Cost-utility analysis, discrete-event simulation<br>TAU + CBT vs TAU | Clinical benefits, clinical harms, costs, cost savings | Cost-effective above willingness-to-pay £20 000 threshold per QALY |

*Legend.* CBT: cognitive behavioural therapy; DUP: duration of untreated psychosis; FEP: first-episode psychosis; NBI: supportive and ass needed psychotherapy; OASIS: Outreach and Support in South London; SPI: specific preventive intervention, including pharmacological treatment with antipsychotics and psychological treatment; TRS: treatment-resistant schizophrenia; UHR: ultra-high risk of psychosis; WCST: Wisconsin Card Sorting Test; WAIS-III: Wechsler Adult Intelligence Scale-3rd Edition; TMT: Trail Making Tests. Edited from (Phillips et al. 2009; Valmaggia et al. 2009; Ising et al. 2015; Liu et al. 2015; Perez et al. 2015; Valmaggia et al. 2015; Brimblecombe et al. 2017; Ising et al. 2017; Campion et al. 2019; Fusar-Poli P. et al. 2020; Jin et al. 2020; Wijnen et al. 2020; Yoviene Sykes et al. 2020; Jin et al. 2021; Sizer et al. 2022; Ologundudu et al. 2023).

functioning, suggesting that the access to CHR-P and related help-seeking behaviour before FEP might not be driven by cognitive symptoms (Liu et al. 2015). Regarding outcomes after FEP, one study set in UK showed that CHR-P-T subjects had fewer hospitalisations, fewer involuntary admissions, and shorter duration of untreated illness (Valmaggia et al. 2015). This latter finding was confirmed in one US study (Yoviene Sykes et al. 2020). However, no differences emerged on the length of hospital stay in both the UK and US, and in the US no differences emerged for hospitalisations. We identified one additional study (Fusar-Poli P. et al. 2020) set in UK showing that CHR-P-T subjects were more likely to receive antipsychotic medication (at 3, 6, and 24 months, not at 12 months), be admitted to hospital both informally and on a compulsory basis, and spend more time in hospital compared to FEP-D subjects, highlighting severe clinical outcomes for CHR-P-T. No differences were observed in the likelihood of receiving clozapine.

Regarding cost-effectiveness, the study selection flow of the systematic review of cohort and cost-effectiveness studies regarding psychosis prevention services is reported in eFigure 9. Studies excluded after full-text assessment,

with reason for exclusion, are reported in eTable 11. From initial 2956 hits we ultimately included 11 studies (Phillips et al. 2009; Valmaggia et al. 2009; Ising et al. 2015; Perez et al. 2015; Brimblecombe et al. 2017; Ising et al. 2017; Campion et al. 2019; Jin et al. 2020; Wijnen et al. 2020; Jin et al. 2021; Ologundudu et al. 2023). Details and results of included studies are reported in Table 9. Six studies were set in UK, three in the Netherlands, one in Australia, and one in Canada. Five studies used data that originated from a single RCT comparing CBT with TAU, and simulated cost-effectiveness models of CBT confirming its cost-effectiveness (Ising et al. 2015; 2017; Jin et al. 2020; Wijnen et al. 2020; Jin et al. 2021). One study measured actual costs associated with specific preventive intervention (SPI) versus need-based intervention (NBI), instead showing no difference in costs (Phillips et al. 2009). Another study found that high-intensive interventions strengthening liaison between primary and secondary care for people presenting with early signs of psychosis was cost-effective (Phillips et al. 2009). Two other studies used real-world data from the OASIS psychosis prevention service, London, UK, showing its cost-effectiveness versus standard care (Valmaggia et al. 2009; Campion et al. 2019). One further study measured the costs before versus after receiving an intervention in a psychosis prevention service, again showing cost effectiveness (Brimblecombe et al. 2017). Finally, a simulation study demonstrated that providing treatment to all CHR-P individuals, regardless of their transition risk as assessed by the North American Prodrome Longitudinal Study risk calculator, led to higher quality-adjusted life-years (QALYs) compared to a risk-stratified approach and was found to be cost-effective (Ologundudu et al. 2023).

### 3.2. Grading, guidelines, and recommendations

#### 3.2.1. Grading of evidence

The criteria used to grade the level of evidence, and formulate guidelines are available in Tables 1 and 10.

Grading of evidence and guidelines for prevention of psychosis at intervention- and service-levels are available in Table 11. Table 11 is limited to those interventions with ≥1 study showing the intervention or the service to be superior to the control group on transition to psychosis.

#### 3.2.2. Recommendations

Considering the evidence and its grading an initial list of 12 recommendations was circulated to authors. Scores were ≥4/5 in ≥ 80% of respondents for all 12 recommendations. The recommendations are listed in Table 12 and reported below together with the consensus rates from authors, grouped by service organisation, assessment and risk communication, and intervention level.

Three recommendations were made at service organisation level:

1. Psychosis indicated prevention services might be implemented in close collaboration with early intervention services for psychosis to minimise duration of untreated illness. 90.7% agreed 4 or 5/5.
2. To prevent psychosis, at the mental health service level, intake age criteria should be between 14 to 35. 87.5% agreed 4 or 5/5.
3. To prevent psychosis, mental health services should allow access to persons with cannabis use disorder. 96.9% agreed 4 or 5/5.

Six recommendations were made at the assessment and risk communication level:

1. To identify CHR-P, mental health services staff should be trained to administering and rating CAARMS, SIPS, or future validated interviews such as PSYCHS in clinical settings. 84.4% agreed 4 or 5/5.
2. To identify CHR-P, mental health services staff should use CAARMS, SIPS, or PSYCHS in the future in clinical settings. 84.4% agreed 4 or 5/5.
3. To estimate risk of psychosis, mental health services staff should be trained in using and interpreting psychosis risk calculators in clinical settings. 81.3% agreed 4 or 5/5.
4. To communicate the risk of psychosis, mental health services staff should be trained in communicating the estimate of risk of psychosis in clinical settings. 84.4% agreed 4 or 5/5.
5. To estimate and communicate the risk of psychosis, mental health services staff should use only validated risk calculators, keeping a human-to-human interaction with client. 81.3% agreed 4 or 5/5.
6. To provide comprehensive care, mental health services staff should assess the presence of comorbid mental disorders also in those meeting CHR-P criteria. 100% agreed 4 or 5/5.

Three recommendations were made at intervention level:

1. To prevent psychosis, mental health services staff should offer treatment to reduce use or achieve abstinence of cannabis use (if present). 90.7% agreed 4 or 5/5.

**Table 10.** World federation of societies of biological Psychiatry grading system for levels of evidence.

| Evidence effective/ Grade | Explanation | Evidence not effective/ Grade | Explanation |
|---|---|---|---|
| Strong/ A | At least two independent RCTs with a low risk of bias show efficacy (superiority to placebo, or in the case of psychotherapy studies, superiority to a 'active psychological placebo' in a study with adequate blinding),<br>OR<br>superiority to/equivalent efficacy compared with an established comparator treatment in a 3-arm study with placebo control or in a well-powered non-inferiority trial (only applicable if such a standard treatment exists) with a low risk of bias,<br>AND<br>No negative RCTs with a low risk of bias exist.<br>If there are contradicting results from RCTs, the majority of RCTs AND/OR a meta-analysis with low risk of bias shows efficacy.<br>If there are more than one 'A' treatment options, the decision should be based on head-to-head comparisons or meta-analyses showing superiority of one of the treatments | Strong/ -A | At least two independent, adequately powered RCTs with low risk of bias as detailed on the left show NO efficacy<br>AND<br>no positive RCTs with a low risk of bias exist<br>If there are contradicting results from RCTs, however, the majority of RCTs AND/OR a meta-analysis with very low risk of bias shows NO efficacy |
| Limited/ B | RCT with a moderate risk of bias showing superiority to placebo (or in the case of psychotherapy studies, superiority to a 'active psychological placebo')<br>OR<br>a randomised controlled comparison with a standard treatment without placebo control with a sample size sufficient for a non-inferiority trial with a moderate risk of bias,<br>AND<br>No negative studies exist<br>OR<br>Meta-Analyses with a moderate risk of bias that shows efficacy | Limited/ -B | 1 RCT with a moderate risk of bias showing NO superiority to placebo (or in the case of psychotherapy studies, NO superiority to a 'active psychological placebo')<br>OR<br>LESS efficacy than a standard treatment in an RCT without placebo control with a moderate risk of bias<br>AND<br>No positive studies exist<br>OR<br>Meta-Analyses with a moderate risk of bias that show NO efficacy |
| Low/ C1 | One or more prospective open studies (with a minimum of 10 evaluable patients per group) using a control group, but no randomisation, or using no control group, show efficacy.<br>OR<br>one or more well-conducted case control or cohort studies (with a minimum of 10 evaluable patients) with a moderate probability that the relationship is causal show efficacy<br>OR<br>RCTs AND/OR meta-analyses with a high risk of bias show efficacy | Low/ -C1 | One or more prospective open studies (with a minimum of 10 evaluable patients) using a control group, but no randomisation, or using no control group, show NO efficacy.<br>OR<br>One or more well-conducted case control or cohort studies (with a minimum of 10 evaluable patients) with a moderate probability that the relationship is causal shows NO efficacy<br>OR<br>RCTS AND/OR meta-Analyses with a high risk of bias that show NO efficacy |
| Low/ C2 | Non-analytic studies, e.g. case reports or case series with less than 10 evaluable patients show efficacy in the majority of cases | Low/ -C2 | Non-analytic studies, e.g. case reports or case series with less than 10 evaluable patients show NO efficacy in the majority of cases |
| Low/ C3 | Expert opinions not based on any published data reporting efficacy | Low/ -C3 | Expert opinions not based on any published data reporting NO efficacy |
| No evidence | No sufficient evidence to advise for or against the use of the intervention | No evidence | No sufficient evidence to advise for or against the use of the intervention |

Edited from (Hasan et al. 2019).

2. To provide comprehensive care, mental health services staff should offer evidence-based treatment for comorbid mental disorders also in those meeting CHR-P criteria. 100% agreed 4 or 5/5.
3. To prevent psychosis, mental health services staff should offer treatment for CHR-P status based on patient preference, clinician/centre experience, and following the 'first do no harm' principle. 93.8% agreed 4 or 5/5.

## 4. Discussion

These guidelines update previous guidelines, in light of updated evidence (NICE 2014; Schmidt SJ et al. 2015; Addington et al. 2017), integrating a lived experience and clinical experience-informed a-priori-defined lens that is representative of the clinical and ethical matters related with the indicated prevention of psychosis. All specific interventions including CBT, other psychosocial interventions, biological interventions and combined

**Table 11.** Guidelines for the prevention of psychosis from the World Federation of Societies of Biological Psychiatry and EPI Canada, on interventions with at least one positive randomised controlled trial on transition to psychosis in clinical high risk of psychosis subjects, or at least one study showing cost-effectiveness.

| Intervention | LoE primary outcome | LoE key and other secondary outcomes | Acceptability | Recommendation |
|---|---|---|---|---|
| Cognitive therapy or CBT for psychosis ($k=7$) | No recommendations<br>RCT:<br>3 superior, high RoB<br>3 negative, high RoB<br>MA RCT:<br>6 MA superior, high RoB<br>2 MA negative, some RoB<br>NMA RCT:<br>1 negative, high RoB | No recommendations<br>RCT:<br>3 superior (depressive, anxiety, insomnia symptoms), high/low RoB<br>7 negative, high/low RoB<br>1 inferior (distress), high RoB<br>MA:<br>1 superior, high RoB<br>2 negative, high RoB<br>NMA:<br>1 inferior, high RoB | GOOD<br>5 cost effective | No recommendation |
| Integrated treatment ($k=2$) | No recommendations<br>RCT:<br>2 superior, high RoB<br>1 negative, high RoB<br>MA RCT:<br>3 negative, high RoB<br>3 inferior, high RoB<br>NMA RCT:<br>1 negative, high RoB | No recommendations<br>RCT:<br>1 superior (negative symptoms), high RoB<br>2 negative, high RoB<br>MA:<br>2 negative, high RoB<br>NMA:<br>1 negative, high RoB | NR | No recommendation |
| Risperidone (including SPI) ($k=2$) | No recommendations<br>RCT:<br>1 superior, high RoB<br>1 negative, low RoB<br>MA RCT:<br>5 superior, high RoB<br>3 negative, high RoB<br>NMA RCT:<br>1 negative, high RoB | No recommendations<br>RCT:<br>1 negative, low RoB<br>1 NA<br>MA:<br>2 negative, high RoB<br>NMA:<br>1 inferior, high RoB | POOR<br>Not cost effective (SPI) | No recommendation |
| ω−3 PUFAs ($k=3$) | No recommendations<br>RCT:<br>1 superior, low RoB<br>3 negative, low RoB<br>MA RCT:<br>3 negative, high Rob<br>2 inferior, high RoB<br>NMA RCT:<br>1 negative, high RoB | No recommendations<br>RCT:<br>1 positive (positive, negative, general symptoms, functioning), low RoB<br>2 negative, low RoB<br>1 inferior (functioning), low RoB<br>MA:<br>3 negative, high RoB<br>NMA:<br>1 negative, high RoB | NR | No recommendation |
| Psychosis prevention service<br>/<br>Any intervention | B<br>MA RCT:<br>3 positive pooling different interventions, and no superior intervention in NMA | C1<br>Cohort:<br>1 cohort: mental health improved or stayed the same, fewer hospitalisations, involuntary admission.<br>2 cohort: DUP shortened<br>2 negative: length of hospital stay<br>1 negative: number of hospitalisations<br>1 negative: clozapine<br>1 inferior: informal and involuntary hospital admission, and length in hospital stay | GOOD<br>3 cost-effective | Limited recommendation |

*Legend.* CBT: cognitive-behavioural therapy; LoE: level of evidence; MA: meta-analysis; NA: did not assess; NMA: network meta-analysis; NR: no studies reported; RCT: randomised controlled trial; RoB: risk of bias; SPI: specific prevention intervention.

interventions, had conflicting findings at the individual RCT and meta-analytic level, precluding any possibility of recommending specific interventions for the prevention of psychosis. Some psychological interventions, such as CBT, have been tested more extensively than others and are therefore more likely to be widely available. Evidence on CBT has been mixed, with some studies supporting its superiority to treatment as usual and others not, including a meta-analysis published after our search (Minichino et al. 2025). Notably, specific interventions pooled together outperformed treatment as usual in several separate meta-analyses (Phillips et al. 2009; Preti and Cella 2010; van der Gaag et al. 2013). Moreover, observational evidence showed that psychosis prevention services improved several outcomes compared with other services (Valmaggia et al. 2015; Yoviene

**Table 12.** Clinical recommendations for the prevention of psychosis.

| Recommendations | Evidence |
|---|---|
| **Service organisation** | |
| Psychosis indicated prevention services might be implemented in close collaboration with early intervention services for psychosis to minimise duration of untreated illness | Observational |
| To prevent psychosis, at the mental health service level, intake age criteria should be between 14 to 35. | Observational |
| To prevent psychosis, mental health services should allow access to persons with cannabis use disorder. | Observational |
| **Assessment and risk communication** | |
| To identify CHR-P, mental health services staff should be trained to administering and rating CAARMS, SIPS, or future validated interviews such as PSYCHS* in clinical settings. | Observational |
| To identify CHR-P, mental health services staff should use CAARMS, SIPS, PSYCHS* in clinical settings. | Observational |
| To estimate risk of psychosis, mental health services staff should be trained in using and interpreting psychosis risk calculators in clinical settings. | Consensus only |
| To estimate and communicate the risk of psychosis, mental health services staff should be trained in communicating the estimate of risk of psychosis in clinical settings. | Consensus only |
| To estimate and communicate the risk of psychosis, mental health services staff should use only validated risk calculators, keeping a human-to-human interaction with client. | Consensus only |
| To provide comprehensive care, mental health services staff should assess the presence of comorbid mental disorders also in those meeting CHR-P criteria. | Observational |
| **Intervention** | |
| To prevent psychosis, mental health services staff should offer treatment aiming to abstinence from cannabis use (if present). | Observational |
| To provide comprehensive care, mental health services staff should offer evidence-based treatment for comorbid mental disorders also in those meeting CHR-P criteria. | Observational |
| To prevent psychosis and provide comprehensive care, mental health services staff should offer treatment for CHR-P status based on patient preference, clinician/centre experience, and following the "first do no harm' principle. | Randomised controlled trials |

*Legend*. *: based on future evidence of psychometric properties; CAARMS: Comprehensive Assessment of At-Risk Mental State; CHR-P: clinical high-risk for psychosis; PSYCHS: Positive SYmptoms for CAARMS Harmonised with SIPS; SIPS, Structured Interview for Prodromal Symptoms.

Sykes et al. 2020), and that prevention services, and CBT in particular, were cost-effective (Valmaggia et al. 2009; Ising et al. 2015; Perez et al. 2015; Brimblecombe et al. 2017; Ising et al. 2017; Campion et al. 2019; Jin et al. 2020; Wijnen et al. 2020; Jin et al. 2021). However, given the lack of consistent findings across individual RCTs, and different meta-analyses, these guidelines can make 'limited' recommendations to implement psychosis prevention services, and cannot recommend one specific intervention in individuals at CHR-P among many that have been previously tested.

While RCTs for schizophrenia select a potentially biased sample that is not necessarily representative of the general population (Taipale et al. 2022), there is no evidence of selection/sampling bias in RCTs of individuals at CHR-P for prevention of psychosis, as rates of transition to psychosis do not differ between cohort studies and RCTs (Salazar de Pablo, Davies, et al. 2021). Hence, findings from RCTs included in this review probably can be extended to real-world services. Psychosis prevention services are mainly designed to provide primary indicated prevention in those meeting CHR-P criteria. However, beyond indicated prevention, psychosis prevention services also implement several primary public health prevention strategies (e.g. universal and selective interventions) globally (Estradé et al. 2022). A systematic review including 66 publications on 13 standalone, 40 integrated, three network, and six regional or international surveys of CHR-P services across Europe, Asia, Oceania, Africa, North and South America, providing care to >28 million people, showed that CHR-P services already target social and cultural (16 initiatives), economic (seven initiatives), demographic (six initiatives), environmental events (four initiatives) and neighbourhood (three initiatives) Sustainable Development Goal determinants of mental disorders developed by United Nations Member States (Estradé et al. 2022), indicating that CHR-P services deliver a wide range of public health initiatives aimed at prevention and the promotion of mental well-being, extending beyond the indicated prevention of psychosis. We believe that given the heterogeneous clinical practice across psychosis prevention services, pooling all interventions reflects a diverse portfolio of interventions that are different in quality and superior in intensity from treatment as usual delivered in 'regular' mental health services, which primarily focus on more advanced stages of persistent and severe mental disorders. However, there is the need for more research on individualised and adapted implementation of psychosis prevention services according to given cultural, environmental and resource parameters.

The specific assessment and intervention model to be administered within each psychosis prevention service should be informed by the clinical presentation of each patient, and should be informed by evidence on CHR-P assessment tools, risk factors for psychosis, psychosis risk modelling, concomitant mental disorders, and, importantly, ethical considerations. Some clinical recommendations were nevertheless made based on the evidence review and consensus.

Mental health professionals working in psychosis prevention services should be trained in using the CAARMS or SIPS/SOPS to assess/determine CHR-P status. Recently a novel tool for CHR-P assessment is being tested - i.e. the PSYCHS (Woods SW et al. 2024) – to overcome limitations of CAARMS or SIPS/SOPS, and to provide one unique tool, which should be ideally be adopted once evidence is available regarding its psychometric properties and clinical usability (Brady and Larrauri 2023). It is important that the service organisation accounts for the need of administering such tools, which can be time-consuming but that are needed to define CHR-P. Moreover, abbreviated versions of CHR-P tools are now available such as the Mini-CAARMS (Stefana et al. 2025), reducing administration time.

Communicating risk estimates in medicine is complex. Risk of transition to psychosis can be calculated, yet this should be done exclusively using multivariable, validated, transparent and reproducible clinical prediction models. Moreover, risk models should always be applied in the context of a human-to-human interaction and by mental health professionals that are trained in clinical prediction model interpretation and communication. Overall, communication with patients and families about psychosis risk should include encouraging patients to state their preferences regarding the communication of medical information, respecting requests not to receive certain information, and tailoring disclosure to the individual's needs and expectations (Woods SW et al. 2021), consistently with ethical guidance from the American Medical Association (AMA n.d.). Any communication to patients regarding their risk should be conducted by staff trained in communicating risk, which they should be accountable for.

Cannabis use is a risk factor for schizophrenia, and other mental disorders (Myran, Harrison, et al. 2023; Myran, Pugliese, et al. 2023; Myran et al. 2024; Myran, Pugliese, Harrison, et al. 2025; Myran, Pugliese, McDonald, et al. 2025). It has been estimated that the population attributable fraction of cannabis with respect to schizophrenia spectrum disorders is 9.73% (95% CI = 4.50–17.30%) (Dragioti et al. 2022). The risk is particularly elevated in young males, and progressively increases from persons with cannabis use disorder to cannabis-induced psychosis (Myran, Harrison, et al. 2023). Considering the age at onset of psychosis, and other mental disorders (Solmi, Radua, et al. 2022), young adults should be informed regarding the risk of cannabis. Unfortunately, the literacy regarding the risk of psychosis associated with use of cannabis is very low (Goodman and Hammond 2022).

Several treatments have been tested for the treatment of cannabis use disorder. Evidence suggests that combining CBT, motivational enhancement therapy (which seeks to enhance motivation to change), and contingency management (which uses operant conditioning to reinforce a target behaviour) is effective in reducing frequency and quantity of use. However, improvements in sustained abstinence remain limited. In this context, testing novel pharmacological agents represents a promising avenue to enhance the effects of existing psychosocial treatments (Sherman and McRae-Clark 2016).

To prevent psychosis and avert adverse developmental effects of presenting symptoms, comorbidities and functional disabilities, psychosis prevention services should not leave out patients younger than 18. The peak age at onset of schizophrenia is 20.5 years, and a reasonable age intake criterion is age 14 to 35 also considering feasibility and resource allocation, as well as specificities of younger populations who frequently need care for different conditions (Solmi, Radua, et al. 2022). Indeed, the high rates of comorbid mental disorders in CHR-P call for a transdiagnostic mental health assessment. Individuals meeting CHR-P criteria should be assessed for and receive evidence-based treatment for concomitant mental disorders targeting also an improvement of functioning. The choice of specific interventions offered to individuals at CHR-P should be based on the person's autonomy and informed shared decision-making and consent process, on a 'first do no harm' non-maleficence principle, and on clinical expertise of a multi-professional mental health team. Regarding comorbid disorders, we could not recommend specific interventions to improve outcomes in CHR-P youth with specific comorbid mental health disorders due to the lack of meta-analytic evidence. Moreover, non-psychotic symptoms (e.g. depressive and anxiety symptoms) have not shown improvement in experimental interventions compared to control conditions in 'generic' samples (i.e. samples not stratified by comorbid mental disorders) of CHR-P individuals. Hence the treatment of comorbid mental disorder should follow evidence-based guidelines for each disorder.

Given that young people with mental health conditions tend to face substantial delays in accessing treatment (McGorry et al. 2024), it is essential to foster continuity of care and strengthen referral pathways, for example by promoting connections with emerging

youth-oriented primary care transdiagnostic services (McGorry et al. 2022).

However, risk estimates need to be communicated in even more cautious and balanced ways in younger subjects. The question whether psychosis prevention services or transdiagnostic mental health services should be implemented remains currently unanswered (Solmi, Soardo, et al. 2023).

Future research should address several aspects that could complement the evidence that informed these guidelines. First, clinicians, ethics experts, subjects with lived experience and their families should work together in co-designing a standardised approach to communicate risk of psychosis. Second, more research needs to be conducted regarding the impact of cannabis strength (i.e. THC content), frequency and quantity of use, on the risk of psychosis and on the outcome of psychosis (after onset) in subjects with or without CHR-P. Third, additional treatments should be conducted to prevent psychosis in CHR-P, testing novel biological pharmacological, non-pharmacological (e.g. brain stimulation), lifestyle (e.g. exercise, diet, smoking cessation), digital or psychosocial interventions. Future multi-arm, adaptive RCTs or implementation science approaches may represent a future direction in the field. Fourth, RCTs are needed to test candidate interventions to prevent psychosis in subjects with cannabis use disorder. Fifth, data from previous RCTs to prevent psychosis in CHR-P should be shared in collaborative efforts to analyse individual patient data to identify subgroups of patients that might benefit from a specific type of treatment. Sixth, while implementing cluster RCTs comparing psychosis prevention service versus transdiagnostic mental health prevention services would pose feasibility barriers, (simulation) studies leveraging data from existing services, and/or Delphi studies collecting the input of persons with lived experience in co-designing prevention services are needed. Seventh, our recommendations were not informed by neuroimaging and biomarker findings, as they are not yet informative for guiding real-world clinical care at scale (Rambaud et al. 2022) due to their small effect sizes, limited replication, lack of evidence testing their clinical utility, and poor scalability. Nevertheless, machine learning approaches and biomarker research may hold promise in advancing knowledge on heterogeneity among youth at CHR-P (Koutsouleris et al. 2021). Future studies employing multimodal and promptly available, scalable parameters may leverage neuroimaging data alongside behavioural and symptom data to refine prognostic precision in this population, in line with ongoing large-scale international initiatives such as the Accelerating Medicines Partnership (AMP®) Schizophrenia (SCZ) program (Brady and Larrauri 2023; Wannan et al. 2024). Eighth, additional studies testing the prognostic accuracy and broader clinical utility of interviews measuring basic symptoms, potentially at even earlier stages than attenuated psychotic symptoms, accounting for language- and context-specific considerations, should be conducted (Schultze-Lutter et al. 2012). Ninth, research focusing on both psychosis prevention services and transdiagnostic prevention services is still limited. To date, tools to assess bipolar at-risk status are being developed (Salazar de Pablo et al. 2025; Stefanelli et al. 2025), as well as even broader approaches such as the clinical high at risk mental state (CHARMS) (McGorry et al. 2018; Destrée et al. 2024), and transdiagnostic prediction models are emerging (Arribas et al. 2026), yet no comparative study has analysed the clinical utility of a transdiagnostic versus a psychosis-focused prevention approach. Tenth, future research could focus on therapeutic monitoring of pharmacological treatment in CHR-P subjects who receive a pharmacological (non-antipsychotic) treatment for comorbid non-psychotic mental disorders. Such research could help develop and examine tools to optimise treatment personalisation. This is in line with recent research advances on therapeutic monitoring of antipsychotic medications in individuals with full-blown psychotic disorders (Hart et al. 2024; Schoretsanitis et al. 2024).

These guidelines have several limitations related with the restrictions of the currently available data, and of previous evidence synthesis efforts. For instance, the recommendation to target cannabis use was not based on evidence demonstrating that a reduction in cannabis use results in lower psychosis transition rates. It was based on the convincing evidence of cannabis as a modifiable risk factor for psychosis. Moreover, prevention in specific populations, such as first-degree relatives of persons with schizophrenia not meeting criteria for CHR-P, individuals with 22q11 syndrome, or those who have not been assessed with CHR-P tools or that do not have cannabis use disorder go beyond the aims and scope of these guidelines.

Nevertheless, we the current guidelines provide context, content, tools and specific guidance that is useful for researchers, clinicians, health care administrators and other interest who aim at reducing the risk for individuals to develop psychosis.

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## Author contributions

Conceptualisation: MS; Methodology: MS, CUC, AFC, TB, GLB; Writing - Original draft: MS, GLB, TB; Visualisation: MS, GLB, RG, TB; Investigation: MS, GLB, TB, RG; Supervision: MS, CUC, AFC; Project administration: MS; Writing - review & Editing: all authors

## Disclosure statement

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## ORCID

Marco Solmi http://orcid.org/0000-0003-4877-7233
Gabriele Lo Buglio http://orcid.org/0000-0003-2425-8383
Howard C. Margolese http://orcid.org/0000-0002-3912-0566
Liang-Jen Wang http://orcid.org/0000-0002-5320-1151
Scott W. Woods http://orcid.org/0000-0002-3103-5228
Michael Berk http://orcid.org/0000-0002-5554-6946

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