**SUPPLEMENTARY MATERIAL**

**eTable 1:** PRISMA 2020 item checklist………..…..…..…..…..…..…..…..…..…..…..…..…..….…..…..…..…..…..….…..…..…..…..………...…page 2

**eTable 2:** MOOSE checklist …..…..…..…..…..…..…..…..…..…..…..…..…..…..…..…..…..…..…..…..….…..…..…..…..…..….…..…………....page 6

**eTable 3:** Risk of bias (quality) assessment using the modified Newcastle Ottawa Scale for cohort studies …..…..…..…..…...……..…..…..page 8

**eTable 4:** Characteristics of the included studies.…..…..…..…..…..…..…..…..…..…..…..…...…..…..…..…..….…..…..…..….…....…...…...…page 9

**eTable 5:** Comparison sociodemographic, comorbidity and treatment characteristics observational cohorts and RCTs……….………...…..page 15

**eTable 6:** Meta-regressions transition to psychosis and moderating factors………….....…….…..…..…..…..…..…..…..…………..…..…..….page 17

**eMethods 1:** CHR-P instruments included..…..…..…..…..…..…..…..…..…..…..…..…..…..…..….…..…..…..…..…..…..….…..…..…..……..page 19

**eMethods 2:** Data extraction details…..…..…..…..…..….…..…..…..…..…..….…..…..…..…..…..….…..…..…..…..………….….…..…..…....page 20

**eMethods 3:** Risk of bias (quality) assessment using the Cochrane Risk of Bias tool…..…..…..…..….……..…..…..…..….……..…..…..…..page 21

**This supplementary material has been provided by the authors to give readers additional information about their work.**

**eTable 1: PRISMA 2020 item checklist**

|  |  |  |  |
| --- | --- | --- | --- |
| **Section and topic**  | **Item #**  | **Checklist item**  | **Location where item is reported** |
| **TITLE**  |  |
| Title  | 1  | Identify the report as a systematic review or a meta-analysis | Title |
| **ABSTRACT**  |   |
| Structured summary  | 2  | See the PRISMA 2020 for Abstracts checklist (table 2) | Abstract |
| **INTRODUCTION**  |  |
| Rationale  | 3  | Describe the rationale for the review in the context of existing knowledge. | Introduction |
| Objectives  | 4  | Provide an explicit statement of the objective(s) or question(s) the review addresses. | Introduction |
| **METHODS**  |
| Eligibility criteria  | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | Methods, eMethods 1 |
| Information sources  | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | Methods  |
| Search strategy | 7  | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | Methods  |
| Selection process | 8  | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | Methods  |
| Data collectionprocess | 9  | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | Methods  |
| Data items  | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | Methods, eMethods 2 |
| 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding source). Describe any assumptions made about any missing or unclear information. | Methods, eMethods 2 |
| Study risk of biasassessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | Methods, eTable 3, eMethods 3 |
| Effect measures  | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | Methods |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | Methods |
| 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | Methods |
| 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | Methods |
| 13d | Describe any methods used to synthesise results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | Methods |
| 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, metaregression). | Methods |
| 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesised results.Reporting bias assessment. | Methods |
| Reporting biasassessment | 14  | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | Methods |
| Certainty assessment | 15  | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome | Methods |
| **RESULTS**   |
| Study selection  | 16a  | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram (see fig 1). | Results, figure 1 |
| 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | Methods, results |
| Study characteristics  | 17 | Cite each included study and present its characteristics. | eTable 4 |
| Risk of bias within studies  | 18 | Present assessments of risk of bias for each included study | eTable 4 |
| Results of individual studies  | 19  | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | Results, table 1-2, eTable 5 |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | Results, eTable 4 |
| 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | Results, Table 1-2, eTable 5 |
| 20c | Present results of all investigations of possible causes of heterogeneity among study results. | Results, eTable 6 |
| 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesised results | N.a. |
| Reporting biases | 21  | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | Results, eTable 4 |
| Certainty of evidence  | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | Results, Table 1-2, eTable 5 |
| **DISCUSSION**   |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | Discussion |
| 23b | Discuss any limitations of the evidence included in the review. | Discussion |
| 23c | Discuss any limitations of the review processes used. | Discussion |
| 23d | Discuss implications of the results for practice, policy, and future research | Discussion |
| **OTHER INFORMATION**  |
| Registration andprotocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | Methods |
| 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | Methods |
| 24c | Describe and explain any amendments to information provided at registration or in the protocol. | Does not apply |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | Discussion |
| Competing interests | 26 | Declare any competing interests of review authors | Discussion |
| Availability of data,code, and othermaterials | 27  | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | Discussion |

**PRISMA 2020 item checklist Abstract**

|  |  |  |  |
| --- | --- | --- | --- |
| **Section and topic**  | **Item #**  | **Checklist item**  | **Location/explanation** |
| **TITLE**  |  |
| Title  | 1  | Identify the report as a systematic review | Identified as a meta-analysis |
| **BACKGROUND**  |  |
| Objectives  | 2 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | Abstract |
| **METHODS**  |  |
| Eligibility criteria  | 3 | Specify the inclusion and exclusion criteria for the review. | Abstract |
| Information sources  | 4 | Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched. | Abstract |
| Risk of bias | 5  | Specify the methods used to assess risk of bias in the included studies. | Not specified because of limited space (250 words) |
| Synthesis of results | 6  | Specify the methods used to present and synthesise results. | Abstract |
| **Results**  |  |
| Included studies | 7 | Give the total number of included studies and participants and summarise relevant characteristics of studies. | Abstract |
| Synthesis of results | 8 | Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured). | Abstract |
| **Discussion**  |  |
| Limitations of evidence | 9 | Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision). | Not specified because of limited space (250 words) |
| Interpretation | 10 | Provide a general interpretation of the results and important implications. | Abstract |
| **Other**  |  |
| Funding | 11 | Specify the primary source of funding for the review. | Not specified because of limited space (250 words) |
| Registration  | 12  | Provide the register name and registration number. | Not specified because of limited space (250 words) |

**eTable 2: MOOSE checklist.**

|  |  |
| --- | --- |
| **Criteria** | **Brief description of how the criteria were handled in the meta-analysis** |
| **Reporting of background should include** |
| √ | Problem definition | No meta-analysis has compared transitions to psychosis in CHR-P individuals between observational cohorts and randomised clinical trials. |
| √ | Hypothesis statement | We hypothesized that patients recruited into RCTs are less unwell and have lower transition than studies in observational/ naturalistic settings. |
| √ | Description of study outcomes | Description of study outcomes are detailed in eMethods 1-2. |
| √ | Type of exposure or intervention | We included original articles that reported the risk of transition in CHR-P individuals. |
| √ | Type of study designs used | Randomised clinical trials and observational cohorts. |
| √ | Study population | CHR-P individuals defined according to established instruments, see eMethods 1. |
| **Reporting of search strategy should include** |
| √ | Qualifications of searchers | The credentials of the investigators are indicated in the author list. |
| √ | Search strategy, including time period included in the synthesis and keywords | Multi-step literature search detailed in the methods section, until 1st November 2020. |
| √ | Databases and registries searched | Pubmed and Web of Science database (Clarivate Analytics), including the Web of Science Core Collection, BIOSIS Citation Index, KCI-Korean Journal Database, MEDLINE, Russian Science Citation Index, and SciELO Citation Index as well as Cochrane Central Register of Reviews, and Ovid/PsychINFO databases. |
| √ | Use of hand searching | We hand-searched bibliographies of retrieved papers and published reviews for additional references. |
| √ | List of citations located and those excluded, including justifications | Details of the literature search process are outlined in the results section and in the PRISMA flowchart (figure 1) |
| √ | Method of addressing articles published in languages other than English | We only included articles in English. |
| √ | Method of handling abstracts and unpublished studies | We looked for both abstracts and unpublished studies in the database and registries detailed above. We contacted authors from the studies with limited data to gather more information. |
| √ | Description of any contact with authors | We contacted corresponding authors and authors from to request additional data when needed. |
| **Reporting of methods should include** |
| √ | Description of relevance or appropriateness of studies assembled for assessing the hypothesisto be tested | Our inclusion/ exclusion criteria, including the designs selected are appropriate to answer our research question. |
| √ | Rationale for the selection and coding of data | Data extraction is in accordance with the population characteristics, study design, exposure, outcome, and possible effect of confounders. |
| √ | Assessment of confounding | Meta-regressions were carried out as detailed in the main text. |
| √ | Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results | We used a modified version of the Newcastle-Ottawa Scale, previously used in the CHR-P field for the longitudinal observational cohorts. We used The Cochrane Risk of Bias tool for the randomised clinical trials. |
| √ | Assessment of heterogeneity | Heterogeneity was assessed with the I2 index and the Q statistic. |
| √ | Description of statistical methods in sufficient detail to be replicated | Statistical methods are detailed in the methods section so they can be replicated.  |
| √ | Provision of appropriate tables and graphics | Both tables and graphics are provided in the main text and supplementary material. |
| **Reporting of results should include** |
| √ | Graph summarizing individual study estimates and overall estimate | Graphs summarizing individual study estimates and overall estimate are appended. |
| √ | Table giving descriptive information for each study included | Our eTable IV provides descriptive information for each study included. |
| √ | Results of sensitivity testing | Sensitivity analysis are reported as detailed in the methods section. |
| √ | Indication of statistical uncertainty of findings | All our meta-analysis include standard deviations or 95% Cis. |
| **Reporting of discussion should include** |
| √ | Quantitative assessment of bias | We did not evaluate publication bias because studies included in the meta-analyses of proportions are non-comparative, thus there are no “negative” or “undesirable” results or study characteristics like significant levels that may have biased publications [1, 2]. |
| √ | Justification for exclusion | We excluded studies about other conditions because the purpose of our review was to see the transition of CHR-P individuals. Our exclusion criteria aim to obtain the highest quality evidence possible.  |
| √ | Assessment of quality of included studies | An assessment of quality of included studies is provided in the main text and supplementary text. |
| **Reporting of conclusions should include** |
| √ | Consideration of alternative explanations for observed results | We have discussed alternative explanations for our findings in the discussion of the text. |
| √ | Generalization of the conclusions | We have addressed the generalization of the conclusions in the discussion of the manuscript. |
| √ | Guidelines for future research | We have suggested guidelines for future research in the discussion of the manuscript. |
| √ | Disclosure of funding source | No separate funding was necessary for the undertaking of this meta-analysis. Conflicts of interest for all the coauthors and funding sources were detailed. |

**eTable 3: Risk of bias (quality) assessment using the modified Newcastle Ottawa Scale for cohort studies.**

|  |  |
| --- | --- |
| **Criteria** | **Maximum Score** |
| Representativeness of exposed cohort (e.g. total population or random sample, selected group) | 1 |
| Method used to ascertain exposure is robust? | 1 |
| Exposed and unexposed are matched or there is an adjustment for confounding factors?  | 2 |
| Assessment of outcome was blind to exposure status or used record linkage, were robust tools used? | 2 |
| Follow-up period was sufficiently long for outcomes to occur? | 1 |
| Loss to follow-up rate is reported, low (<30%), and same in exposed and non-exposed? | 1 |

**eTable 4: Characteristics of the included studies.**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **First author and year of publication** | **Country** | **Study design** | **CHR-P subgroups** | **CHR-P sample size** | **Age: mean, SD (range)** | **% of female** | **CHR-P assessment tools** | **Duration of follow up** | **NOS/****RoB2**a |
| Addington 2011 [3] | USA | Randomised clinical trial | 100% APS | 51 | 20.9 (4.1), 14-30 | 29.4 | SIPS/SOPS | 18 | High risk |
| Amminger 2010 [4] | Austria | Randomised clinical trial | 90.1% APS, 43.2% BLIPS, 7.4% GRD | 81 | 16.4 (2.1), 13-25  | 67.0 | PANSS | 12 | Low risk |
| Amminger 2015 [5] | Austria | Randomised clinical trial | 90.1% APS, 43.2% BLIPS, 7.4% GRD | 81 | 16.4 (2.1), 13-25  | 67.0 | PANSS | 3 | Low risk  |
| Atkinson 2017 [6] | Australia | Observational cohort | N.a. | 102 | 18.6 (2.7), 13-25 | 53.9 | CAARMS | 12 | 5 |
| Bang 2019 [7] | Korea | Observational cohort | 97.4% APS, 15.6% BLIPS, 15.6% GRD | 77 | 19.9 (3.4), 15-32 | 40.3 | SIPS/SOPS | 25.8b | 4 |
| Barbato 2013 [8] | Multi | Observational cohort | 98.7% APS, 2% GRD | 151 | 19.7 (4.7), 12-21 | 43.7 | SIPS/SOPS | 6 | 4 |
| Barbato 2014 [9] | Multi | Observational cohort | 97.4% APS, 1.3% GRD | 153 | 19.7 (4.2) | 42.1 | SIPS/SOPS | 6 | 3 |
| Bechdolf 2012 [10] | Germany | Randomised clinical trial | 27.3% GRD, 96.1% BS | 128 | 26.0 (5.8) | 36.7 | ERIraos | 24 | High risk |
| Bechdolf 2017 [11] | Germany | Randomised clinical trial | N.a. | 280 | 24.4 (5.1), 18-49 | 34 | SIPS/SOPS, SPI-A | 12 | Unclear risk |
| Beck 2019 [12] | Switzerland | Observational cohort | N.a. | 255 | 24.1 (8.2), 14-57 | 59.0 | SIPS/SOPS | 192 | 3 |
| Bolt 2019 [13] | Multi | Observational cohort | N.a. | 294 | 19.1 (4.5) | 54.4 | CAARMS | 40.8b | 5 |
| Bourgin 2020 [14] | France | Observational cohort | N.a. | 27 | 17.6 (3.7), 15-25 | 14.8 | CAARMS | 22.4b | 3 |
| Brewer 2012 [15] | Australia | Observational cohort | N.a. | 219 | 25.8 (5.1), 15-30 | N.a. | CAARMS | 24 | 4 |
| Bruene 2011 [16] | Germany | Observational cohort | N.a. | 10 | 25.5 (5.3) | 30.0 | SIPS/SOPS | 12 | 4 |
| Brucato 2018 [17] | USA | Observational cohort | N.a. | 200 | 20.1 (3.9), 13-30 | 28.0 | SIPS/SOPS | 24 | 5 |
| Cadenhead 2017 [18] | USA | Randomised clinical trial | N.a. | 127 | N.a. | N.a. | SIPS/SOPS | 6 | Unclear risk |
| Cadenhead 2018 [19] | USA | Randomised clinical trial | N.a. | 127 | N.a. | N.a. | SIPS/SOPS | 24 | Unclear risk |
| Carrion 2017 [20] | USA | Observational cohort | N.a. | 92 | 15.9 (2.1), 12-22 | 37.0 | SIPS/SOPS | 12 | 5 |
| Catalan 2020 [21] | Multi | Observational cohort | 83.2% APS, 6.9% BLIPS, 16.2% GRD | 303 | 22.5 (4.6),15-35 | 48.2 | CAARMS | 24 | 4 |
| Chan 2019 [22] | Singapore | Observational cohort | 60% APS, 2.7% BLIPS, 21.2% GRD, 16.1% Combined  | 255 | 20.8 (3.3), 16-30 | 32.2 | CAARMS | 24 | 5 |
| Chen 2016 [23] | China | Observational cohort | 100% APS  | 63 | 21.9 (4.5), 14-30 | 47.6 | SIPS/SOPS | 6 | 4 |
| Chung 2018 [24] | Australia | Observational cohort | N.a. | 275 | 17.3 (3.1) | 38.5 | SIPS/SOPS | 12 | 4 |
| Conrad 2017 [25] | Australia | Observational cohort | 69.1% APS, 16.2%, BLIPS, 26.2% GRD | 191 | 17.5 (3.0), 12-25 | 42.9 | CAARMS | 120 | 5 |
| Cornblatt 2015 [26] | USA | Observational cohort | 100% APS | 101 | 15.9 (2.2), 12-22 | 30.8 | SIPS/SOPS | 60 | 6 |
| Damme 2019 [27] | USA | Observational cohort | N.a. | 73 | 18.6 (1.8), 13-22 | 39.7 | SIPS/SOPS | 12 | 4 |
| DeVylder 2013 [28] | USA | Observational cohort | 100% APS, 1.5% BLIPS, 4.6% GRD | 65 | 19.5 (3.7), 12-30 | 23.1 | SIPS/SOPS | 48 | 5 |
| Francesconi 2017 [29] | Italy | Observational cohort | N.a. | 67 | 24.5 (3.4), 17-31 | 42.2 | CAARMS | 36 | 5 |
| Friedman-Yakoobian 2020 [30] | USA | Randomised Clinical trial | N.a. | 38 | 19.2 (3.0), 15-30 | 26.3 | SIPS/SOPS | 9 | Unclear risk |
| Fusar-Poli 2020 [31] | UK | Observational cohort | 80.4% APS, 18.1% BLIPS, 1.5% GRD | 598 | 22.6 (4.9), 14-35 | 44.7 | CAARMS | 120 | 5 |
| Gaspar 2019 [32] | Chile | Observational cohort | 92.6% APS, 7.4% GRD | 27 | 17.6 (2.9), 12-28 | 29.7 | SIPS/SOPS | 24 | 4 |
| Glenthøj 2020 [33] | Denmark | Observational cohort | 98.6% APS, 2.1% BLIPS, 21.9% GRD | 146 | 23.9 (4.2), 18-40 | 58.2 | CAARMS | 12 | 4 |
| Guo 2019 [34] | USA  | Observational cohort | N.a. | 117 | 16.6 (3.5), 12-25 | 42.7 | SIPS/SOPS | 12 | 4 |
| Hamilton 2019 [35] | USA | Observational cohort | 100% APS, 2.3% BIPS, 2.3% GRD | 43 | 16.9 (3.5), 12.0-26.6 | 37.2 | SIPS/SOPS | 28 | 5 |
| Heinze 2018 [36] | UK | Observational cohort | N.a. | 14 | 20.8 (3.1) | 64.3 | CAARMS | 12 | 3 |
| Hengartner 2017 [37] | Switzerland | Observational cohort | 53.2% APS, 3.2% BLIPS, 92.0% BS | 188 | 20.5 (5.8), 13-35 | 39.8 | SIPS/SOPS, SPI-A, SPI-CY | 36 | 4 |
| Hormozpour 2016 [38] | Iran | Observational cohort | N.a. | 50 | 27.5 (5.0), 15-35 | 47.8 | SIPS/SOPS | 12 | 5 |
| Hui 2013 [39] | UK | Observational cohort | 100% APS, 11.7% GRD | 60 | 20.2 (2.9), 16-35 | 48.3 | CAARMS | 12 | 5 |
| Hur 2012 [40] | Korea | Observational cohort | 92.3% APS, 10.8% GRD | 65 | 20.9 (3.9) | 38.5 | CAARMS | 12 | 5 |
| Iftimovici 2020 [41] | France | Observational cohort | N.a. | 133 | 21.0 (4.0), 16-30 | N.a. | CAARMS | 12 | 5 |
| Kantrowitz 2015 [42] | USA | Randomised clinical trial | N.a. | 35 | 19.4 (4.1), 13-35 | 34.3 | SIPS/SOPS | 4 | Unclear risk |
| Keri 2009 [43] | Hungary | Observational cohort | 100% APS, 100% BLIPS, 55.2% GRD | 67 | 21.2 (3.6) | 46.3 | CAARMS | 12 | 6 |
| Kleineidam 2019 [44] | Germany  | Observational cohort | N.a. | 160 | 25.7 (6.7) | 32.5 | ERIraos | 24 | 6 |
| Kline 2015 [45] | USA | Observational cohort | N.a. | 21 | 16.2 (3.1), 12-22 | 65.0 | SIPS/SOPS | 6 | 5 |
| Kotlicka-Antczak 2017 [46] | Poland | Observational cohort | 76.5% APS, 4.9% BLIPS, 38.3% GRD | 81 | 18.7 (3.5), 15-32 | 51.9 | CAARMS | 62 | 6 |
| Kraan 2018 [47] | Multi | Observational cohort | 85.7% APS, 5.8% BLIPS, 15.8% GRD | 259 | 22.7 (4.5), 15-35 | 46.1 | CAARMS | 24 | 4 |
| Kristensen 2020 [48] | Denmark | Randomised clinical trial | N.a. | 111 | 23.8 (4.2),18-40 | 53.2 | CAARMS | 6.5 | Low risk |
| Labad 2015 [49] | Spain | Observational cohort | 61.5% APS, 17.9% BLIPS, 20.5% GRD | 39 | 22.3 (4.6) | 30.8 | CAARMS | 12 | 5 |
| Lam 2018 [50] | Singapore | Observational cohort  | N.a. | 173 | 21.3 (3.5), 14-29 | 32.4 | CAARMS | 24 | 4 |
| Landa 2016 [51] | USA | Randomised clinical trial | 66.7% APS, 16.7% BLIPS, 16.7% GRD | 6 | 19.5 (1.5), 17-21 | 66.7 | CAARMS | 3 | High risk |
| Lee 2013 [52] | Singapore | Observational cohort | 83.2% APS, 3.5% BLIPS, 28.3% GRD | 173 | 21.3 (3.5), 14-29 | 32.4 | CAARMS | 24 | 5 |
| Lemos-Giraldez 2009 [53] | Spain | Observational cohort | 85.2% APS, 4.9% BLIPS, 9.8% GRD | 61 | 21.7 (3.8), 15-31 | 34.4 | SIPS/SOPS | 36 | 5 |
| Leon-Ortiz 2017 [54] | Mexico | Observational cohort | N.a. | 33 | 19.6 (4.1) | 21.2 | SIPS/SOPS | 24 | 6 |
| Lindgren 2014 [55] | Finland | Observational cohort | 98.1% APS, 5.5% GRD | 54 | 16.7 (0.8), 15.2-18.1 | 81.5 | SIPS/SOPS | 12 | 5 |
| Liu 2011 [56] | Taiwan | Observational cohort | N.a. | 59 | 21.5 (4.0), 16-32 | 44.1 | SIPS/SOPS | 52.8 | 6 |
| Matsumoto 2019 [57] | Japan | Observational cohort | 95.1% APS, 11% BLIPS, 20.4% GRD | 309 | 21.4 (5.5), 14-40 | 61.5 | CAARMS, SIPS/SOPS | 60 | 5 |
| McFarlane 2014 [58] | USA | Randomised clinical trial | N.a. | 148 | 16.6 (3.2), 12-35 | 47 | SIPS/SOPS | 24 | High risk |
| McGlashan, 2006 [59] | USA | Randomised clinical trial | N.A. | 60 | 17.7 (4.8), 12-36 | 35.0 | SIPS/SOPS | 24 | Unclear risk |
| McGorry 2017 [60]c | Multi | Randomised clinical trial | N.A. | 304 | 19.2 (4.6) | 54.3 | CAARMS | 12 | Unclear risk |
| McGorry, 2002 [61] | Australia | Randomised clinical trial | N.A. | 59 | 20.0 (4.0), 14-28 | 42.4 | CAARMS | 12 | High risk |
| McGorry, 2013 [62] | Australia | Randomised clinical trial | N.A. | 115 | 18.0 (3.0) | 60.9 | CAARMS | 12 | Unclear risk |
| Miklowitz 2014 [63] | USA | Randomised clinical trial | N.a. | 129 | 17.4 (4.1), 12-32 | 42.6 | SIPS/SOPS | 6 | High risk |
| Morcillo 2015 [64] | UK | Observational cohort | 100% APS, 11.7% GRD | 60 | 19.9 (2.4), 16-35 | 48.3 | CAARMS | 24 | 7 |
| Morrison 2004 [65] | UK | Randomised clinical trial | 82.8% APS, 10.3% BLIPS, 6.9% GRD | 58 | 21.0 (5.0), 16-36 | 31.0 | PANSS | 12 | High risk |
| Morrison 2012 [66] | UK | Randomised clinical trial | N.a. | 288 | 20.7 (4.3), 14-35 | 37.5 | CAARMS | 24 | High risk  |
| Nelson 2011 [67] | Australia | Observational cohort | 81.3% APS, 4.4% BLIPS, 25.6% Trait | 817 | N.a. (median: 14), 14-29 | 59.0 | CAARMS | 6 | 5 |
| Niles 2019 [68] | USA | Observational cohort | 100% APS | 223 | 16.7 (4.1), 12-35 | 40.2 | SIPS/SOPS | 24 | 5 |
| Ohmuro 2016 [69] | Japan | Observational cohort | 97.2% APS, 19.4% GRD | 36 | 20.9 (4.7), 14-35 | 61.1 | CAARMS | 25.6b | 4 |
| Osborne 2019 [70] | USA | Observational cohort | N.a. | 68 | 18.6 (1.8), 13-21 | 41.2 | SIPS/SOPS | 24 | 4 |
| Pelizza 2020 [71] | Italy | Observational cohort | 89.6% APS, 5.2% BLIPS, 5.2% GRD | 97 | 18.8 (4.3),13-35 | 54.6 | CAARMS | 24 | 4 |
| Pelletier-Baldelli 2017 [72] | USA | Observational cohort | N.a. | 53 | 18.8 (1.6), 12-21 | 39.6 | SIPS/SOPS | 12 | 3 |
| Poletti, 2019 [73] | Italy | Observational cohort | 70.6% APS, 3.9% BLIPS, 2% GRD, 84.3% BS  | 51 | 15.4 (1.6), 13-18 | 58.8 | CAARMS, SPI-CY | 24 | 5 |
| Pontillo 2019 [74] | Italy | Observational cohort | N.a. | 75 | 14.6 (5.1), 6-27 | 41.3 | SIPS/SOPS | 12 | 5 |
| Pozza 2020 [75] | Italy | Randomised clinical trial | 100% APS, 5.2% BLIPS, 13.8% GRD | 58 | 25.7 (6.0), 16-35 | 32.8 | CAARMS | 14 | Unclear risk |
| Pruessner 2012 [76] | Canada | Observational cohort | 83.3% APS, 3.3% BLIPS, 13.3% GRD | 30 | 20.3 (3.2) | 46.7 | CAARMS | 12 | 4 |
| Pruessner 2017 [77] | Canada | Observational cohort | 80.8% APS, 5.1% BLIPS, 14.1% GRD | 177 | 19.3 (4.0), 14-35 | 38.9 | CAARMS | 24 | 4 |
| Quijada 2015 [78] | Spain | Observational cohort | N.a. | 38 | 16.7 (5.9), 12-39 | 23,7 | SIPS/SOPS | 12 | 4 |
| Ryan 2018 [79] | Multi | Observational cohort | 92.8% APS, 3% BLIPS, 11% GRD | 1093 | 18.4 (4.4) | N.a. | SIPS/SOPS | 24 | 4 |
| Sakuma 2018 [80] | Japan | Observational cohort | 93.3% APS, 6.7% BLIPS, 11.1% GRD | 45 | 21.0 (5.0), 14-35 | 60.0 | CAARMS | 12 | 5 |
| Sasabayashi 2020 [81] | Japan | Observational cohort | N.a. | 107 | 21.3 (5.4) | 54.2 | CAARMS, SIPS/SOPS | 90 | 4 |
| Sawada 2017 [82] | Japan | Observational cohort | N.a. | 47 | 19.9 (3.5), 12-30 | 52.9 | SIPS/SOPS | 54 | 5 |
| Schlosser 2012 [83] | USA | Observational cohort | 77.5% APS, 20.2% BLIPS, 2.4% GRD | 84 | 16.9 (3.5) | 38.0 | SIPS/SOPS | 24 | 4 |
| Schultze-lutter 2014 [84] | Germany | Observational cohort | N.a. | 246 | 25.3 (6.6) | 38.2 | SIPS/SOPS, BSABS, SPI-A | 48 | 4 |
| Simon 2012 [85] | Switzerland | Observational cohort | 93.2% APS, 4.1% BLIPS, 2.7% GRD, 35.6% BS | 73 | 20.4 (5.2), 14-40 | 39,7 | SIPS/SOPS | 24 | 4 |
| Stain 2016 [86] | Australia | Randomised clinical trial | 80.7% APS, 7.0% BLIPS, 33.3% GRD | 57 | 16.3 (2.9) | 59.7 | CAARMS | 12 | High risk |
| van der Gaag 2012 [87] | Netherlands | Randomised clinical trial | N.a. | 201 | 22.7 (5.5), 14-35 | 50.7 | CAARMS | 18 | High risk |
| Velthorst 2013 [88] | Netherlands | Observational cohort | 89.9% APS, 6.8% BIPS, 4.1% GRD, 25% BS | 148 | 17.2 (3.8) | 35.8 | SIPS/SOPS, BSABS-P | 51 | 4 |
| von Hohenberg 2014 [89] | USA | Observational cohort | 89.3% APS, 14.3% GRD | 28 | 20.6 (3.9), 13-35 | 36.0 | SIPS/SOPS | 12.3 | 5 |
| Wang 2020 [90] | China | Observational cohort | N.a. | 18 | 24.6 (5.8) | 33.3 | SIPS/SOPS | 48 | 3 |
| Welsh 2014 [91] | UK | Observational cohort | 100% APS, 13.3% GRD | 30 | 15.8 (1.4), 12-18 | 53.0 | CAARMS | 24 | 4 |
| Woodberry 2013 [92] | USA | Observational cohort | 94% APS, 17% GRD | 53 | 16.0 (2.4), 12-25 | 51.0 | SIPS/SOPS | 23b  | 4 |
| Woods 2017 [93] | USA | Randomised clinical trial | N.a. | 51 | 16-40 | N.a. | SIPS/SOPS | 6 | Low risk |
| Yung 2011 [94]  | Australia | Randomised clinical trial | N.A. | 115 | 18.0 (3.0) | 60.9 | CAARMS | 6 | High risk |
| Zhang 2018 [95] | China | Observational cohort | N.a. | 511 | 20.6 (6.2), 14-45 | 52.8 | SIPS/SOPS | 24 | 4 |
| Ziermans 2011 [96] | Netherlands | Observational cohort | N.a. | 72 | 15.3 (1.9), 12-18 | 38. | SIPS/SOPS | 24 | 4 |

aNOS was applied to observational cohorts; RoB was applied to randomised clinical trials; bMean duration of follow-up; cYoun 2019 [97] larger observational cohorts was excluded because of overlap.

APS: Attenuated Psychosis Symptoms; BLIPS: Brief Limited Intermittent Psychotic Symptoms; BS: Basic symptoms; BSABS: Bonn Scale for the Assessment of Basic Symptoms; BSIP: Basel Screening Instrument for Psychosis; CAARMS: Comprehensive Assessment of At Risk Mental States; ERIraos: Early Recognition Inventory; GRD: Genetic risk and deterioration syndrome; NOS: Newcastle-Ottawa Scale; PANSS: Positive and Negative Syndrome Scale; RoB2: Version 2 of the Cochrane risk-of-bias tool for randomised trials; SIPS: Structured Interview for Prodromal Syndromes; SOPS: ; SPI-A: Schizophrenia Proneness Instrument–Adult; SPI-CY: Schizophrenia Proneness Instrument–Child and Yo

**eTable 5: Comparison sociodemographic, comorbidity and treatment characteristics observational cohorts and RCTs**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Outcome** | **Type** | **n of studies (total****sample)** | **Effect size** | **Heterogeneity** | **Within subgroup heterogeneity** |
| **Mean** | **95%CI** | **Z score** | **P value** | **Q** | **I2** | **P value** | **Q** | **P** |
| **Age** | **All** | **73 (9179)** | **20.0** | **19.5-20.5** | **74.0** | **<0.001** | **4713.3** | **98.5** | **<0.001** | **0.037** | **0.848** |
| RCT | 14 (872) | 20.1 | 18.4-21.8 | 21.9 | <0.001 | 1135.6 | 98.9 | <0.001 |
| Cohorts | 59 (8,307) | 20.0 | 19.4-20.5 | 70.5 | **<0.001** | 3558.6 | 98.4 | <0.001 |
| **Outcome** | **Type** | **n of studies (total****sample)** | **Effect size** |  | **Within subgroup heterogeneity** |
| **%** | **95%CI** | **Z score** | **P value** | **Q** | **I2** | **P value** | **Q** | **P** |
| **Sex (proportion of female)** | **All** | **72 (8,220)** | **44.9** | **43.8-45.9** | **-9.5** | **<0.001** | **374.1** | **81.0** | **<0.001** | **0.772** | **0.380** |
| RCT | 14 (936) | 43.6 | 41.3-45.9 | -5.4 | <0.001 | 109.5 | 87.2 | <0.001 |
| Cohorts | 58 (7,284) | 45.2 | 44.0-46.4 | -7.9 | <0.001 | 263.2 | 78.7 | <0.001 |
| **Proportion of APS** | **All** | **36 (4,745)** | **83.5** | **82.3-84.7** | **35.6** | **<0.001** | **354.7** | **90.1** | **<0.001** | **1.687** | **0.193** |
| RCT | 4 (126) | 84.7 | 79.1-89.0 | 8.8 | <0.001 | 5.9 | 49.7 | 0.113 |
| Cohorts | 32 (4,619) | 83.5 | 82.1-84.7 | 34.5 | <0.001 | 348.7 | 91.1 | <0.001 |
| **Proportion of BLIPS/BIPS** | **All** | **36 (4,745)** | **6.8** | **5.0-9.2** | **-15.9** | **<0.001** | **236.5** | **85.2** | **<0.001** | **0.368** | **0.544** |
| RCT | 4 (126) | 7.8 | 4.6-13.0 | -8.5 | <0.001 | 1.09 | 0.0 | 0.581 |
| Cohorts | 32 (4,619) | 6.4 | 4.4-9.2 | -13.4 | <0.001 | 234.5 | 86.4 | <0.001 |
| **Proportion of GRD** | **All** | **36 (4,745)** | **11.4** | **8.6-15.0** | **-12.8** | **<0.001** | **301.6** | **88.7** | **<0.001** | **0.025** | **0.875** |
| RCT | 4 (126) | 12.3 | 4.6-29.0 | -3.6 | <0.001 | 21.5 | 86.0 | <0.001 |
| Cohorts | 32 (4,619) | 11.3 | 8.4-15.1 | -12.3 | <0.001 | 280.0 | 89.3 | <0.001 |
| **Proportion of mood disorders** | **All** | **12 (1,090)** | **39.3** | **35.1-43.6** | **-4.8** | **<0.001** | **152.4** | **92.8** | **<0.001** | **1.829** | **0.176** |
| RCT | 3 (234) | 38.4 | 34.1-42.8 | -5.0 | <0.001 | 1.0 | 0.0 | 0.616 |
| Cohorts | 9 (856) | 49.1 | 34.4-64.0 | -0.1 | 0.913 | 145.5 | 94.5 | <0.001 |
| **Proportion of anxiety disorders** | **All** | **24 (4,180)** | **29.0** | **23.4-35.4** | **-6.0** | **<0.001** | **380.0** | **94.0** | **<0.001** | **0.040** | **0.842** |
| RCT | 4 (263) | 27.4 | 14.5-45.8 | -2.4 | <0.001 | 38.0 | 92.1 | <0.001 |
| Cohorts | 20 (3,917) | 29.3 | 23.2-36.2 | -5.5 | <0.001 | 317.7 | 94.0 | <0.001 |
| **Proportion of other substance use disorders**a | **All** | **9 (1,411)** | **15.9** | **12.7-19.9** | **-12.1** | **<0.001** | **28.4** | **71.8** | **<0.001** | **5.6** | **0.018** |
| RCT | 1 (29) | 3.4 | 0.8-12.7 | -4.6 | <0.001 | 0.0 | 0.0 | <0.001 |
| Cohorts | 8 (1,382) | 16.8 | 13.3-21.0 | -11.4 | <0.001 | 21.9 | 68.1 | <0.001 |
| **Proportion of antipsychotics at baseline**b | **All** | **32 (3,089)** | **24.0** | **19.3-29.4** | **-8.2** | **<0.001** | **433.6** | **92.8** | **<0.001** | **1.184** | **0.277** |
| RCT | 2 (186) | 20.9 | 14.7-28.8 | -6.1 | <0.001 | 0.0 | 1.0 | <0.001 |
| Cohorts | 30 (2,903) | 26.5 | 20.0-34.1 | -5.5 | <0.001 | 427.5 | 93.0 | <0.001 |
| **Proportion of antidepressants at baseline** | **All** | **18 (1,788)** | **29.8** | **24.2-36.1** | **-5.9** | **<0.001** | **113.0** | **84.1** | **<0.001** | **0.033** | **0.855** |
| RCT | 3 (111) | 31.7 | 14.6-55.8 | -1.5 | <0.001 | 22.7 | 91.2 | <0.001 |
| Cohorts | 15 (1,677) | 29.6 | 23.8-36.2 | -5.7 | <0.001 | 90.2 | 83.4 | <0.001 |
| **Proportion of other psychotropics at baseline** | **All** | **13 (1,267)** | **16.7** | **10.7-25.0** | **-6.2** | **<0.001** | **179.3** | **92.7** | **<0.001** | **0.026** | **0.873** |
| RCT | 1 (29) | 17.2 | 9.5-29.1 | -4.5 | <0.001 | 1.0 | 0.0 | <0.001 |
| Cohorts | 12 (1,238) | 16.0 | 8.1-29.2 | -4.2 | <0.001 | 179.2 | 93.3 | <0.001 |

aExcluding alcohol use disorders and cannabis use disorder; bSensitivity analysis for % antipsychotics at follow-up could not be estimated due to limited data for RCTs.

**eTable 6: Meta-regressions transition to psychosis and moderating factors**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Factor (reference)** | **No. of****Studies** | **β Coefficient** | **SE** | **95% CI** | **Z-Value** | **P value** |
| *Study design*:(Cohort)RCT | 74 | -0.0359 | 0.2262 | -0.4792 | 0.4074 | -0.1585 | 0.8740 |
| Mean age | 73 | -0.0134 | 0.0303 | -0.0461 | 0.0729 | 0.4401 | 0.6598 |
| Proportion of females | 72 | -0.0022 | 0.0103 | -0.0223 | 0.0179 | -0.2116 | 0.8324 |
| Proportion of APS | 36 | 0.0089 | 0.0094 | -0.0094 | 0.0273 | 0.9527 | 0.3407 |
| Proportion of BLIPS/BIPS | 36 | 0.0182 | 0.0045 | 0.0094 | 0.0270 | 4.0589 | **<0.0001** |
| Proportion of GRD | 36 | 0.0125 | 0.0091 | -0.0054 | 0.0303 | 1.3676 | 0.1714 |
| Proportion of Basic symptoms | 3 | D.n.a. a |
| Year of publication | 74 | -0.0422 | 0.0291 | -0.0992 | 0.0148 | -1.4524 | 0.1464 |
| CHR-P assessment instrument:(CAARMS)SIPSOthers | 74 | -0.06010.2325 | 0.18940.3621 | -0.4313-0.4772 | 0.31110.9422 | -0.31750.6442 | 0.75090.5207 |
| Quality of the study (RoB2):(High risk of bias)Unclear risk of biasLow risk of bias | 15 | 0.13730.8871 | 0.38640.7100 | -0.6200-0.5044 | 0.89462.2788 | 0.35541.2495 | 0.72230.2115 |
| Quality of the study (NOS) | 59 | 0.1859 | 0.1062 | -0.0223 | 0.3942 | 1.7501 | 0.0801 |
| *Continent*: (Asia) EuropeNorth AmericaSouth AmericaAustraliaMore than one | 74 | 0.2105-0.0275-0.1813-0.3111-0.3461 | 0.24400.25910.92140.44450.5355 | -0.2677-0.5353-1.9872-1.1825-1.3957 | 0.68870.48041.62460.56010.7036 | 0.8627-0.1060-0.1968-0.7000-0.6462 | 0.38830.91560.84400.48390.5181 |
| Duration of untreated attenuated psychotic symptoms | 2 | D.n.a.a |
| Proportion of baseline ICD/ DSM comorbid disorders | Any non-psychotic mental disorder | 4 | D.n.a.a |
| Any mood disorder | 12 | 0.0007 | 0.0085 | -0.0159 | 0.0173 | 0.0813 | 0.9352 |
| Major depressive disorder | 5 | D.n.a.a |
| Bipolar disorders | 5 | D.n.a.a |
| Personality disorders | 4 | D.n.a.a |
| Neurodevelopmental disorders | 5 | D.n.a.a |
| Anxiety disorders | 24 | 0.0084 | 0.0089 | -0.0091 | 0.0258 | 0.9367 | 0.3489 |
| ADHD | 2 | D.n.a.a |
| Cannabis use disorder | 4 | D.n.a.a |
| Alcohol use disorder | 3 | D.n.a.a |
| Other substance use disorderb | 9 | -0.0449 | 0.0590 | -0.1605 | 0.0707 | -0.7615 | 0.4463 |
| PTSD | 5 | D.n.a.a |
| OCD | 8 | 0.0149 | 0.0229 | -0.0299 | 0.0597 | 0.6531 | 0.5137 |
| Proportion of interventions | Antipsychotics baseline | 32 | 0.0069 | 0.0120 | -0.0166 | 0.0305 | 0.5760 | 0.5646 |
| Antipsychotics at follow-up | 12 | 0.0141 | 0.0078 | -0.0012 | 0.0294 | 1.8033 | 0.0713 |
| Antidepressants at baseline | 18 | -0.0215 | 0.0228 | -0.0663 | 0.0234 | -0.9377 | 0.3484 |
| Antidepressants at follow-up | 3 | D.n.a.a |
| Other psychotropics at baseline | 13 | -0.0246 | 0.0236 | -0.0709 | 0.0217 | -1.0421 | 0.2974 |
| Other psychotropics at follow-up | 3 | D.n.a.a |
| Psychotherapy at baseline | 5 | D.n.a.a |
| Psychotherapy at follow-up | 3 | D.n.a.a |
| Needs-based-intervention at baseline | 6 | D.n.a.a |
| Needs-based-intervention at follow-up | 2 | D.n.a.a |

aD.N.A: does not apply due to lack of enough studies (<6 studies) providing this data to evaluate its influence; bExcluding alcohol use disorders and cannabis use disorder.

ADHD: Attention Deficit and Hyperactivity Disorder; APS: Attenuated Psychosis Symptoms; BLIPS: Brief Limited Intermittent Psychotic Symptoms; BS: Basic symptoms; CAARMS: Comprehensive Assessment of At Risk Mental States; GRD: Genetic risk and deterioration syndrome; DSM: Diagnostic and Statistical Manual of Mental Disorders; ICD: International classification of diseases; OCD: obsessive compulsive disorder; PTSD: Posttraumatic stress disorder; RCT: randomised controlled trial; SIPS: Structured Interview for Prodromal Syndromes.

**eMethods 1: CHR-P instruments included (modified from) [98]**

The CHR-P state comprises the Ultra High Risk state and/or the Basic Symptoms [98].

* The following UHR instruments were considered to define the UHR state: Comprehensive Assessment of At-Risk Mental States (CAARMS) [99] and Structured Interview for Psychosis-risk Syndromes (SIPS) [100, 101] and Early Recognition Inventory (ERIraos) [102]. Furthermore, before the development of these instruments, the CHR-P state was defined through the Positive and Negative Syndrome Scale (PANSS) [103], Brief Psychiatric Rating Scale (BPRS) [104].
* The following UHR instruments were considered to define the BS [98]: Bonn Scale for the Assessment of Basic Symptoms (BSABS) [105], Basel Screening Instrument for Psychosis (BSIP) [106], and Schizophrenia Proneness Instrument [107] - Adult (SPI-A) and Child and Youth (SPI-CY) version -.
* Transition to psychosis was operationalised as defined by each CHR-P instruments or according to ICD/DSM-any version

**eMethods 2: Study measures**

**A) Measures describing the main characteristics of the studies included:**

* First author and year of publication
* Country
* Study design (Observational cohort, Randomised clinical trial)
* Proportion of Attenuated Psychosis Symptoms -APS-
* Proportion of Brief Limited Intermittent Psychotic Symptoms -BLIPS-
* Proportion of Genetic risk and deterioration syndrome -GRD-
* Proportion of Basic symptoms -BS-
* CHR-P sample size
* Mean age (SD or range)
* Proportion of females
* CHR-P assessment instrument (as listed in eMethods 1)
* Duration of follow up (in months)
* Study quality: NOS and RoB scores

**B) Planned meta-regressor factors that may affect transition risk:**

* Year of publication, study design, proportion of APS, BLIPS, GRD, BS, mean age, proportion of females, CHR-P assessment tools, study quality
* Continent: Europe, Asia, North America, South America, Australia, More than one
* Duration of untreated attenuated psychotic symptoms – in months- (as per Fusar-Poli 2012) [108]
* Proportion of baseline comorbid mental disorders (all ICD or DSM-defined): a) any non-psychotic mental disorder; b) any mood disorder c) major depressive disorder; d) bipolar disorders; e) personality disorders; f) neurodevelopmental disorders; g) anxiety disorders; h) ADHD; i) cannabis use disorder; j) alcohol use disorder; k) other substance use disorder; l) PTSD; m) OCD
* Proportion of interventions at baseline and follow-up: a) antipsychotics, b) antidepressants, c) other psychotropics, d) psychotherapy [including CBT, IPT and other psychotherapeutic interventions], e) needs-based-intervention (as previously defined i.e. encompassing: supportive psychotherapy primarily focusing on pertinent issues such as social relationships and vocational or family problems; case management, providing psychosocial assistance with accommodation, education or employment; brief family psychoeducation and support).

**eMethods 3: Risk of bias (quality) assessment using the Cochrane Risk of Bias tool**

The Cochrane Risk of Bias tool [109] was used to assess and classify the risk of bias in each of the included studies, as per criteria defined a priori.

A judgement was made about whether each study had a high, low or unclear risk of bias in each of the following six domains: random sequence generation, allocation concealment, blinding of participants and study personnel, blinding of outcome assessments, incomplete outcome data, and selective outcome reporting.

The overall risk of bias was classified as low if none of the above domains was rated as high risk and three or less were rated as unclear risk. It was classified as moderate if one domain was rated as high risk, or none rated as high risk but four or more rated as unclear risk. All other studies were classified as having a high risk of bias [110].

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