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

**eTable1. Diagnostic Criteria for Ultra-high risk clinical High-Risk for Psychosis (CHR-P) criteria according to SIPS/SOPS1,2.**

|  |  |  |  |
| --- | --- | --- | --- |
| CHR-P | Attenuated psychotic symptoms | Brief limited intermittent psychotic symptoms | Genetic risk and deterioration syndrome |
| Symptoms | SIPS positive symptom scales: (P1) unusual thought content, (P2) suspiciousness, (P3) grandiose ideas, (P4) perceptual abnormalities, and (P5) disorganized communication, with at least 1 of these symptoms rated 3, 4, or 5, indicating clinically significant disturbance below a psychotic level of intensity. | SIPS positive symptom scales: (P1) unusual thought content, (P2) suspiciousness, (P3) grandiose ideas, (P4) perceptual abnormalities, and (P5) disorganized communication, with at least 1 of these symptoms rated, 6 indicating clinically severe disturbance with psychotic features. | The patient meets criteria for Schizotypal Personality Disorder OR has a first-degree relative with a psychotic disorder. |
| Frequency | Symptoms ever been present at an average frequency of at least once per week over a month. | Symptoms ever been present at least several minutes per day, at least one month. |  |
| Onset | Symptoms should have begun within the past year OR currently rate one or more scale points higher compared to 12 months before. Symptoms that occurred over the past month only are rated. | Symptoms should have reached a psychotic level of intensity in the previous 3 months. |  |
| Level of functioning | No social/occupational dysfunction requirement. | No social/occupational dysfunction requirement. | 30% drop in GAF score over the last month as compared to 12 months before. |
| Duration |  | Up to 3 months. |  |
| SIPS: Structured Interview of Psychosis-risk Syndromes; SOPS: Scale of Prodromal Symptoms. | | | |

**eTable2. Diagnostic criteria for Basic Symptoms3,4.**

|  |  |  |
| --- | --- | --- |
| Basic Symptoms | COPER | COGDIS |
| BS are subtle, subjectively experienced disturbances in mental processes including thinking, attention, perception, speech, stress tolerance, and affect. | Presence of at least any one of the following ten basic symptoms, with at least weekly occurrence within the last three months and first occurrence at least 12 months ago:   * Thought interference. * Thought perseveration. * Thought pressure. * Thought blockages. * Disturbance of receptive speech. * Decreased ability to discriminate between ideas and perception, fantasy and true memories. * Unstable ideas of reference. * Derealisation. * Visual perception disturbances. * Acoustic perception disturbances. | Presence of at least any two of the following nine basic symptoms, with at least weekly occurrence within the last three months:   * Inability to divide attention. * Thought interference. * Thought pressure. * Thought blockages. * Disturbance of receptive speech. * Disturbance of expressive speech. * Unstable ideas of reference. * Disturbances of abstract thinking. * Captivation of attention by details of the visual field. |
| BS are regarded as an immediate symptomatic expression of the neurobiological processes underlying psychosis and the earliest form of self‐experienced symptoms. |
| Two criteria for the identification of basic symptoms:   * Cognitive‐Perceptive Basic Symptoms (COPER). * Cognitive Disturbances (COGDIS). |

**eTable3. PRISMA 2020 Statement and Checklist.**

| **Section and Topic** | **Item #** | **Checklist item** | **Location where item is reported** |
| --- | --- | --- | --- |
| **TITLE** | | |  |
| Title | 1 | Identify the report as a systematic review. | Title page |
| **ABSTRACT** | | |  |
| Abstract | 2 | See the PRISMA 2020 for Abstracts checklist. | Abstract page |
| **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 |
| 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. | eMethods 1 |
| 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 collection process | 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. | eMethods 2 |
| 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | eMethods 2 |
| Study risk of bias assessment | 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. | 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 synthesize 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, meta-regression). | Methods |
| 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | Methods |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | eMethods 3 |
| 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. | Results, figure 1 |
| 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | NA |
| Study characteristics | 17 | Cite each included study and present its characteristics. | eTable 7-8 |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | eTable 7-8 |
| 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, tables |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | Results |
| 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, figure 2-3 |
| 20c | Present results of all investigations of possible causes of heterogeneity among study results. | Results, table 2 |
| 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | Results, Table 2 |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | Results |
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | Results |
| **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, eDiscussion |
| 23c | Discuss any limitations of the review processes used. | Discussion, eDiscussion |
| 23d | Discuss implications of the results for practice, policy, and future research. | Discussion |
| **OTHER INFORMATION** | | |  |
| Registration and protocol | 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. | NA |
| 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 other materials | 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 |

**eTable4.** **PRISMA 2020 Abstract Checklist.**

| **Section and Topic** | **Item #** | **Checklist item** | **Reported (Yes/No)** |
| --- | --- | --- | --- |
| **TITLE** | | |  |
| Title | 1 | Identify the report as a systematic review. | Yes |
| **BACKGROUND** | | |  |
| Objectives | 2 | Provide an explicit statement of the main objective(s) or question(s) the review addresses. | Yes |
| **METHODS** | | |  |
| Eligibility criteria | 3 | Specify the inclusion and exclusion criteria for the review. | Yes |
| Information sources | 4 | Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched. | Yes |
| Risk of bias | 5 | Specify the methods used to assess risk of bias in the included studies. | Yes |
| Synthesis of results | 6 | Specify the methods used to present and synthesise results. | Yes |
| **RESULTS** | | |  |
| Included studies | 7 | Give the total number of included studies and participants and summarise relevant characteristics of studies. | Yes |
| 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). | Yes |
| **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). | Yes |
| Interpretation | 10 | Provide a general interpretation of the results and important implications. | Yes |
| **OTHER** | | |  |
| Funding | 11 | Specify the primary source of funding for the review. | No |
| Registration | 12 | Provide the register name and registration number. | Yes |

**eTable5. 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 assessed the proportion of negative symptoms in children and adolescents with an EOP diagnosis/at CHR-P. |
| √ | Hypothesis statement | We hypothesized that children adolescents with an EOP diagnosis/ in a CHR-P state would have frequently negative symptoms. |
| √ | Description of study outcomes | Proportion of EOP and CHR-P children and adolescents with negative symptoms. |
| √ | Type of exposure or intervention used | We included individual studies that reported the presence of negative symptoms in EOP/CHR-P in children and adolescents. |
| √ | Type of study designs used | Cross-sectional studies, longitudinal cohort and intervention studies. |
| √ | Study population | Children and adolescents with an EOP diagnosis/in a CHR-P state. |
| **Reporting of search strategy should include** | |  |
| √ | Qualifications of researchers | The credentials of the investigators are indicated in the author list and in the acknowledgements. |
| √ | Search strategy, including time period included in the synthesis and keywords | We performed a multi-step literature search using the following keywords: (“child\*” OR “adolesc\*” OR “paediatric” OR “pediatric” OR “teen” OR “early-onset” OR “EOP”) AND (“psychosis” OR “schizophrenia” OR “schizoaffective” OR “prodrom\*” OR “ultra-high risk” OR “clinical high risk” OR “clinical high-risk” OR “attenuat\*” OR “APS” OR “high risk” OR “high-risk” OR “BLIPS” OR “brief limited” OR “brief intermittent” OR “genetic high risk” OR “genetic high-risk” OR “GRD” OR “at risk mental state” OR “at-risk mental state” OR “risk of progression” OR “progression to first-episode” OR “basic symptoms”) AND “negative symptoms”. |
| √ | Databases and registries searched | PubMed and Web of Science database (Clarivate Analytics): Web of Science Core Collection. BIOSIS Citation Index. KCI-Korean Journal Database. MEDLINE. Russian Science Citation Index, and SciELO Citation Index. Cochrane Central Register of Reviews, “Schizophrenia International Research Society” (SIRS) and Early Intervention in Mental Health international conference (IEPA), clinicaltrials.gov, WHO International Clinical Trials Registry Platform (ICTRP). |
| √ | Use of hand searching | We hand-searched bibliographies of retrieved papers 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. |
| √ | Method of addressing articles published in languages other than English | Articles in any language were selected. We received the support from international collaborators and we used translation online tools (E.g. google translator). |
| √ | Method of handling abstracts and unpublished studies | Original individual studies and conference proceedings/abstracts were included. Reviews, editorials and clinical cases were excluded. |
| √ | Description of any contact with authors | We did not contact corresponding authors to request additional data for this study. |
| **Reporting of methods should include** | |  |
| √ | Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested | Detailed inclusion and exclusion criteria were described in the methods section. |
| √ | Rationale for the selection and coding of data | Data extracted from each of the studies were relevant to the population characteristics, study design, comparison group, exposure and outcomes. |
| √ | Assessment of confounding factors | Confounding factors were assessed as part of the meta-regressions analyses. |
| √ | Assessment of study quality. | We used a previously validated version of the Newcastle-Ottawa Scale for the evaluation of cross-sectional and cohort studies. |
| √ | Assessment of heterogeneity | Heterogeneity was assessed with the I2 index and sources of heterogeneity were evaluated through the sensitivity analyses. |
| √ | Description of statistical methods in sufficient detail to be replicated | Statistical methods are described in detail in the methods section. |
| √ | Provision of appropriate tables and graphics | We included the PRISMA flow-chart and several tables and graphics to describe the literature search and our results. |
| **Reporting of results should include** | |  |
| √ | Graph summarizing individual study estimates and overall estimate | We have included figures summarizing individual study estimates and overall estimates. |
| √ | Table giving descriptive information for each study included | We have presented descriptive information for each study in the supplementary material. |
| √ | Results of sensitivity testing | Subgroup analyses were conducted as specified. |
| √ | Indication of statistical uncertainty of findings | We reported 95% CI in our analyses. |
| **Reporting of discussion should include** | |  |
| √ | Quantitative assessment of bias | Publication biases were assessed with Egger test. The trim and fill method was used to correct the estimates in the case of publication biases. |
| √ | Justification for exclusion | Exclusion criteria and justification are described in the manuscript. |
| √ | Assessment of quality of included studies | Our discussion and limitations take into consideration the amount of evidence and its quality. |
| **Reporting of conclusions should include** | |  |
| √ | Consideration of alternative explanations for observed results | We discussed other explanations for our findings in the discussion section. |
| √ | Generalization of the conclusions | We have addressed the generalization of the conclusions in the discussion section. |
| √ | Guidelines for future research | We have suggested possible streams of future development and research in oyr discussion. |
| √ | Disclosure of funding source | Funding source described at the end of the manuscript. No separate funding was necessary for the undertaking of this systematic review and meta-analysis. |

**eTable6. Risk of bias (quality) assessment using modified Newcastle Ottawa Scale for cross-sectional and cohort studies.**

|  |  |
| --- | --- |
| **Criteria** | **Maximum Score** |
| *Cross Sectional Studies* | |
| Sample representative of target sample (e.g. all eligible or random sample)? | 2 |
| Sample size justified and satisfactory? | 1 |
| Non-response rate is defined satisfactory, and characteristics of responders/non-responders compared? | 1 |
| Ascertainment of exposure (i.e. menstrual cycle) is valid and/or well described? | 1 |
| Assessment of outcome with robust tool and/or record linkage? | 2 |
| Outcome per group reported appropriately? | 1 |
| *Cohort Studies* | |
| Representativeness of exposed cohort (e.g. total population or random sample. selected group) | 1 |
| Method used to ascertain exposure (menstrual cycle phase) is robust? | 1 |
| Exposed and unexposed are matched or 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 (e.g. more than one menstrual cycle? | 1 |
| Loss to follow-up rate is reported. low (<30%). and same in exposed and non-exposed? | 1 |

**eTable7. Characteristics of included studies (samples with EOP individuals only).**

| **Author and year of publication** | **Country** | **Study design, (NOS score, RoB score- if applicable-)** | **Sample size EOP** | **Mean age±SD, (range), years** | **Males, %** | **Instruments used (EOP/ negative symptoms)** | **Key findings** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Alaghband-Rad 19975 | USA | Cross-sectional, (4) | 29 | 10.2**±**1.5 (10-19) | N.a. | DSM-III-TR / SANS | A correlation between negative symptoms and smaller total cerebral volume was found (r=-0.65, p<0.001). Adjusting for IQ did not change the results significantly (r=0.64, p=0.002). Total cerebral volume accounted for 31% of the variance in negative symptoms (p=0.004). |
| Alfimova 20216 | Rusia | Cross-sectional, (6) | 75 | 10.2**±**3.5 | 83 | ICD-10 / PANSS | The allele A of ZNF804A was associated with greater severity of negative symptoms in EOP (p<0.05). Negative symptoms were more severe in EOP than adult-onset psychosis (p< 0.05). |
| Arango 20127 | Spain | Longitudinal, (6) | 61 | 15.5**±**1.7 (12-18) | 65.6 | K-SADS-Pl DSM-IV / PANSS | There was an association between left frontal CSF volume change during follow-up (r=0.58; p=0.003) and left parietal CSF change (r=0.45; p=0.03) with negative symptoms in individuals with schizophrenia. |
| Bellgrove 20068 | Australia | Cross-sectional, (4) | 21 | 15.3**±**2.6 | 57.1 | K-SADS-Pl DSM-IV / PANSS | The undifferentiated schizophrenia group had higher negative symptom scores than the paranoid schizophrenia group (p=0.05). |
| Bunk 19999 | Ger | Longitudinal, (3) | 44 | N.a. | 43.2 | PANSS / PANSS | Negative symptoms remained stable after 42 years (p=0.935) as opposed to positive symptoms (p<0.001) and general symptoms (p=0.002) which did improve. |
| Burton 201910 | USA | Longitudinal, (5) | 318 | 17.0**±**3.3 | 62.3 | SIPS/SOPS / SIPS/SOPS | Negative symptoms were associated to poorer social functioning (p<0.001) and role functioning (p=0.003). There was an interaction between positive symptoms and negative symptoms (p=0.001) where positive symptoms decreased the association between negative symptoms and social functioning. |
| Calderon-Mediavilla 202111 | Spain | Cross-sectional, (6) | 62 | 16.1**±**1.11 (13-18) | 59.7 | DSM-V/ PANSS | Negative symptoms were more severe in EOP individuals with higher levels of depression (p=0.023). A relationship was found between the dysphoria scale and some negative symptoms: social withdrawal (r=0.262; p=0.04) and active social avoidance (r=0.298;p=0.019). |
| Calvo 201412 | Spain | RCT, (7, unclear risk of bias) | 55 | 16.4**±**8.0 | 61.8 | DSM-IV / PANSS | The psychoeducation group showed a greater reduction in negative symptoms after treatment compared to the non-structured group (r=0.41, p<0.05). |
| Calvo 201513 | Spain | RCT, (7, unclear risk of bias) | 55 | 16.4**±**8.0 | 61.8 | DSM-IV / PANSS | After the two-year follow-up, no statistically significant differences were observed between EOP individuals in the psychoeducation group and those in the non-structured group in terms of negative symptoms (p>0.05). |
| Cheng 202114 | China | Cross-sectional, (7) | 216 | 10.7**±**2.2 | 41.7 | ICD-10 / PANSS | Compared with adult-onset schizophrenia, EOP individuals had more severe negative symptoms (p=0.02). Negative symptoms at admission were predictors of poor treatment efficacy in EOP individuals (OR=0.945, p=0.009). |
| Cohen 200415 | Israel | Cross-sectional, (4) | 30 | 17.1 (13-21) | 80 | DSM-IV / PANSS, BPRS | There was a significant correlation between negative symptoms and test phase response time (r=0.44, p=0.015). Individuals with higher negative symptoms responded more slowly than those with lower scores. |
| Corcoran 200516 | USA | Cross-sectional, (4) | 26 | 15.0**±**1.8 | 61.5 | DSM-III-R / PANSS | IQ and negative symptoms highly associated with one another (r=0.63, p=0.003). Smell identification deficits were significantly associated with greater negative symptoms (r=0.47, p=0.03), including blunted affect (r=0.51, p=0.02). |
| Correll 200517 | USA | Longitudinal, (5) | 29 | 16.2**±**2.7 (12-22) | 65 | DSM-IV / SIPS/SOPS/ K-SADS-E | 38.4% of individuals had only attenuated negative symptoms or no psychotic symptoms at 6 months follow-up. Brief psychotic disorder was associated with lower maximum levels of negative symptoms compared to psychosis NOS (p=0.02). |
| Bahn 200231 | Korea | Cross-sectional, (4) | 48 | 17.9**±**2.7 | 60.4 | DSM-III-R / PANSS | EOP individuals diagnosed with schizophrenia showed negative symptoms more frequently than late onset schizophrenia (p<0.05). 77% EOP individuals had negative symptoms. |
| Correll 200818 | USA | Longitudinal, (5) | 26 | 15.9**±**2.6 | 65.4 | DSM-IV / SOPS | A correlation was found between higher negative symptoms and shorter follow-up duration (p=0.012). |
| Correll 202219 | USA | RCT, (6, low risk of bias) | 326 | 15.3**±**1.4 | 63.8 | DSM-IV / PANSS | After six weeks, the treatment-naive group did not improve in negative symptoms with lurasidone compared to placebo (p=0.18; ES=0.40). In the previously treated group, treatment with lurasidone was associated with greater improvement versus placebo in negative symptoms (p=0.017; ES=0.32). |
| Craddock 201820 | USA | Cross-sectional, (5) | 124 | 13.3**±**2.7 | 52 | DSM-III-R or DSM-IV / PANSS | Using a two-factor solution containing positive and negative dimensions 29.8% EOP individuals had low scores on both dimensions, 26.6% high negative scores with low positive scores and 44.0% high scores on both dimensions. |
| DeVylder 201321 | USA | Cross-sectional, (7) | 84 | 14.7**±**2.3 | 57.1 | DSM-IV / N.a. | Negative symptoms were increased in the EOP individuals with declining social support compared to the stable social support group (p<0.05). |
| Downs 201922 | UK | Longitudinal, (6) | 638 | (10.0-17) | 51.6 | ICD-10 / PANSS, NLP | The presence of negative symptoms at first episode was significantly associated with multiple treatment failure (adjusted HR=1.62, p=0.02). |
| Duan 202123 | China | Cross-sectional, (5) | 36 | 15.5**±**1.8 (12-18) | 44.4 | DSM-IV-TR / PANSS | Significant negative correlations between the bilateral hippocampal volumes and total negative symptoms (p<0.025). Impairments in verbal memory had an indirect effect mediating the association between negative symptoms in the left hippocampal volume (bootstrap estimate effect=−0.0040) and right hippocampal volume (bootstrap estimate effect=−0.0034). |
| Fields 199424 | USA | Cross-sectional, (4) | 34 | (6.0-16.0) | 61.8 | KIDDIE-PANSS / PANSS | Negative symptoms were more frequent in EOP individuals with schizophrenia admitted into the hospital than in other psychosis (p=0.04). |
| Findling 200325 | USA | Other intervention study (3) | 16 | 13.8**±**1.5 (12-17) | 75 | DSM-IV / PANSS | Negative symptoms improved after treatment with olanzapine in 8-week, open-label, outpatient study (p<0.01). This difference was significant since week six (p<0.01). |
| Fleischhaker 200526 | Germany | Longitudinal, (4) | 81 | n.a. | 55.5 | DSM-III-TR / SANS | EOP individuals with a family history of schizophrenia or schizoaffective disorder compared to those without a family history of schizophrenia or schizoaffective disorder did not have higher scores of negative symptoms (p=0.32). |
| Fraguas 201427 | Spain | Longitudinal, (5) | 66 | 16.2**±**1.64 | 71.2 | DSM-IV / PANSS | Negative symptoms at baseline were associated to executive performance at baseline (β=−4.811, p=0.007). Negative symptoms at baseline predicted an improvement in executive performance after two years (β=4.688, p=0.008). |
| Garcia Traverso 201928 | Spain | Longitudinal, (4) | 110 | 15.5 | N.a. | N.a. / PANSS | Negative symptom dimension was the most consistent and stable component. It was predominant at all but one assessment, accounting for 23.66% of overall variance at baseline, 25.7% at 4 weeks, 13.9% at 6 months 36.3% at 12 months and 40.1% at 24 months. |
| Garcia-Amador 201029 | Spain | Cross-sectional, (3) | 49 | 15 | N.a. | N.a. / PANSS | A higher improvement in negative symptoms correlated with a thinner frontal cortex at baseline (r=0.5, p=0.003). Reduction in negative symptoms correlated with baseline negative symptom severity (r=0.6, p<0.001). |
| Garcia-Amador 202030 | Spain | Longitudinal, (3) | 49 | 15 | N.a. | N.a. / PANSS | Reduction in negative symptoms was positively correlated with baseline negative symptom severity (r=0.6, p< 0.001). Reduction in negative symptoms was positively correlated to frontal cortical thickness (r=0.5, p=0.003). This correlation remained significant after controlling for baseline negative symptom severity (r=0.4, p=0.003). |
| Gerstenberg 201532 | Switzerland | Cross-sectional, (4) | 12 | 14.9**±**1.2 (9.0-19.0) | 58.3 | DSM-IV / PANSS | No association found between negative symptoms and sleep spindle density (p=0.07). |
| Gothelf 200333 | Israel | Other intervention study, (5) | 43 | 14.9**±**1.7 | 62.8 | DSM-IV / PANSS | A significant improvement in negative symptoms was observed after eight weeks: average decline in negative symptoms scores from baseline to week 8 was 14.0% for risperidone, 17.7% olanzapine and 19.2% haloperidol. |
| Hadjez 200334 | Israel | Cross-sectional, (3) | 20 | 16.2**±**2.8 | N.a. | K-SADS-DSM-IV / PANSS | A correlation was found between negative symptoms and emotional expression (r=0.58, p<0.01), involvement (r=0.54, p<0.05) and recall (r=0.48, p<0.05). |
| Hassan 201135 | Egypt | Longitudinal, (5) | 56 | 17**±**3.7 | 46.4 | DSM-IV / PANSS | More impairment in premorbid functioning (p<0.01) and global functioning (p<0.01) were associated with more negative symptoms (p<0.01). The remittent group had less severe negative symptoms (p=0.024). |
| Hemmerle 201036 | German | Other intervention study, (3) | 24 | 16.9**±**1.2 (14-19) | 66.7 | ICD-10 / PANSS | Participants attending a programme of residential outpatient care following discharge from a clinic showed a significantly greater decrease on negative symptoms than the control group (p=0.002). |
| Hintze 201537 | Poland | Cross-sectional, (5) | 33 | 17.3**±**1.2 (15-19) | 60 | ICD-10 / PANSS | No significant differences between EOP individuals with and without a family burden were observed in negative symptoms. A greater intensity of negative symptoms correlated with a lower performance on the WCST evaluating executive functions and working memory (higher percentage of perseverative errors) (r=0.38, p<0.05). Greater intensity of negative symptoms correlated with less % numbers correct and more % of wrong numbers as per the N-back test (r=-47 and r=0.47 both p<0.001). |
| Hollis 200338 | UK | Cross-sectional, (7) | 110 | 14.7**±**1.5 (10-17) | 53 | DSM-III-TR / OPCRIT | The negative symptom dimension was associated with enuresis (OR=1.93, p<0.05) and incontinence during psychosis (OR=3.35, p=0.005). |
| Jarbin 200339 | Sweden | Longitudinal, (5) | 68 | 15.7 (11.8-18.7) | 48.5 | DSM-IV / PANSS | Individuals with stable schizophrenia spectrum disorder had more severe negative symptoms than those with stable affective psychotic disorders (p<0.01). Those whose diagnosis changed to schizophrenia spectrum disorders after a follow up of 10.5 years average had more severe negative symptoms than those with stable affective psychotic disorders (p<0.01) but less severe negative symptoms than those with stable schizophrenia spectrum disorders (p<0.05). |
| Jarbin 200440 | Sweden | Longitudinal, (6) | 88 | 15.7**±**1.5 | 50 | DSM-IV / PANSS | EOP individuals who never attempted suicide had more negative symptoms during first episode (p<0.05). |
| Kafali 201941 | Turkey | Cross-sectional, (5) | 30 | 16.3**±**1.8 (13-19) | 40 | K-SADS-PL DSM-IV / PANSS | The presence of ≥1 negative symptom (OR=1.3, 95% CI=0.5–93.6) and ≥2 negative symptoms (OR=2.75, 95% CI=0.8–9.4) were higher in the EOP than in the BD group. 53.5% EOP had negative symptoms. |
| Karacetin 202242 | Turkey | Cross-sectional, (8) | 101 | 16.3**±**1.3 | 65.3 | DSM-IV-TR / PANSS | Valine/Valine group had a higher score of negative symptoms compared to Valine/Metionine group (p=0.018, d=0.55). |
| Karakus 202243 | Turkey | Longitudinal, (7) | 132 | 14.9**±**1.7 | 33.3 | DSM-V / PANSS | Age at onset was lower in those with persistent negative symptoms (p=0.022). The % of history of suicide attempts was higher in those without persistent negative symptoms (p=0.002). Duration of untreated psychosis was higher in those with persistent negative symptoms (p=0.022). |
| Kemp 201344 | USA | RCT, (6, high risk of bias) | 107 | 12.8**±**3.08 | 62.6 | DSM-IV / PANSS | Less severe negative symptoms were associated with obesity status at baseline (p=0.003). |
| Kim 200945 | Republic of Korea | Other intervention study, (2) | 22 | 14.0**±**2.4 (6.5-16.8) | 54.5 | DSM-IV / N.a. | A greater general response to aripiprazole according to the Clinical Global Impression–Improvement scale was found in those individuals with negative symptoms than in those with positive symptoms (p=0.028; r=–0.47). |
| Kim 201346 | Korea | Cross-sectional, (3) | 16 | 16.2**±**1.8 | 50 | DSM-IV-TR / PANSS | Early onset group also exhibited more negative symptoms (p=0.022) and of more severity (p=0.007) than adult-onset group. There was a correlation between an earlier age of onset with number of negative symptoms (p=0.022) and severity of negative symptoms (p=0.007). |
| Kumra 199647 | USA | RCT, (3, high risk of bias) | 21 | 14.0, 2.4 (6-18) | 52.4 | DSM-IIIR / SANS | Clozapine decreased negative symptoms compared to haloperidol in double blind RCT (p=0.002). |
| Kumra 199848 | USA | RCT, (3, high risk of bias) | 23 | 16.0**±**4.0 | 52.2 | DSM-IIIR / SANS | At week 8 of olanzapine, relative to baseline, there was a 21% improvement in negative symptoms (no comparison group, open label). |
| Kumra 200849 | USA | RCT, (3, high risk of bias) | 39 | 15.6**±**2.1 (10-18) | 53.8 | DSM-IV / SANS | Clozapine was more efficacious in decreasing negative symptoms than olanzapine after 12 weeks (p=0.02, d=0.92). |
| Li 202050 | China | Cross-sectional, (6) | 72 | 14.7**±**1.8 | 33.3 | SCID-DSM-IV / PANSS | A negative correlation was found between negative symptoms and abnormal Dynamic amplitude of low-frequency fluctuations (dALFF) variability of the right middle temporal gyrus (r=-0.2723, p=0.0207). |
| Maki 200851 | Finland | Longitudinal, (1) | n.a. | n.a. | N.a. | N.a. / N.a. | 94% of subjects who got psychosis reported negative symptoms. Negative symptoms were associated with the onset of psychosis. |
| Matsumoto 200152 | UK | Cross-sectional, (4) | 40 | 15.5**±**2.2 (8-17) | 50 | DSM-IV / PANSS | No correlation between whole brain volume and EOP individuals’ negative (r=0.2, p=0.1) symptoms was found. A correlation was found between negative symptoms score and left (r=-0.2. p=0.03) and right (r=-0.02, p=0.04) hippocampal volumes in MRI. |
| McClellan 199953 | USA | Longitudinal, (6) | 51 | 14.9**±**2.0 (9-17) | 65 | DSM-IV / SANS | Individuals with schizophrenia (72%) and schizoaffective disorder (43%) had more negative symptoms at baseline than those with bipolar disorder (21%) or psychosis-NOS (9%). |
| McClellan 199954 | USA | Longitudinal, (6) | 54 | 14.8**±**2.1 | 64.8 | DSM-IV / SANS | Negative symptoms upon entry predicted lower highest level of functioning at one year (β=0.6, p=0.005) and two year follow up (β=0.48, p=0.003). |
| McClellan 200255 | USA | Longitudinal, (6) | 69 | 14.8**±**2.2 | 60.86 | DSM-IV / SANS | IQ was inversely related to negative symptoms (r=–0.41, p<0.05). Those taking antipsychotic agents had more severe negative symp-toms (p<0.01), while those taking lithium had less severe negative symptoms (p<0.005). Negative symptoms upon entry predicted highest level of functioning at one year (β=0.62, p<0.001) and two year follow up (β=0.55, p<0.001)- |
| McClellan 200356 | USA | Longitudinal, (4) | 69 | 14.9**±**2.2 (7-18) | 68 | DSM-IV / PANSS | A correlation was found between introversion on the sociability scale and negative symptoms (r=0.45, p<0.005). A correlation was found between poorer peer relationships and negative symptoms (r=0.26, p<0.005). |
| McConville 200057 | USA | Other intervention study, (1) | 10 | 13.1 (12-17) | 10 | DSM-IV (SCID) / SANS | Negative symptoms improved after 20 days in open-label trial with quetiapine (p=0.0006). |
| McConville 200358 | USA | Other intervention study, (2) | 10 | 13.1 (12-17) | 10 | DSM-IV (SCID) / SANS | Negative symptoms improved in 88-week, open-label trial with quetiapine (p<0.05). |
| Meng 200659 | Multi-country | Cross-sectional, (5) | 56 | 16.2**±**1.4 (12-18) | 51.1 | DSM-IV (SCID) / PANSS | Social functioning was associated with negative symptoms (r=-0.42, p=0.006). More negative symptoms at follow-up were associated with more negative symptoms at baseline (p<0.05) but not with age or gender. |
| Merchan-Naranjo 200760 | Spain | Longitudinal, (2) | 24 | <18 | N.a. | DSM-IV/ PANSS | Negative symptoms at baseline were the only significant variable that predict the functional outcome at the two-year follow-up (p=0.010). |
| Morch-Johnsen 202261 | Norway | Cross-sectional, (7) | 169 | 15.5**±**1.5 (12-18) | 59.2 | DSM-IV (SCID) / PANSS | Negative symptom scores for both apathy (β=−0.257, p=0.002) and diminished expression (β=−0.259, p=0.001) were inversely associated with verbal learning scores. An association was also seen between diminished expression and speed of processing (β=−0.173, p=0.024). |
| Mozes 200662 | Israel | Other intervention study, (4) | 25 | 11.1**±**1.6 (9-14) | 40 | DSM-IV / PANSS | The percentage of children achieving greater than 50% reduction in negative PANSS scores was higher in olanzapine (41.7%) than in risperidone (7.7%) (p=0.047); however, this difference did not remain significant following Bonferroni correction. No difference in symptoms when evaluated continuously (p=0.144). |
| Mueller 202063 | Germany | Other intervention study, (6) | 25 | 17.5**±**1.5 (14-20) | 56 | DSM-IV / PANSS | No differences between CBT+ TAU and TAU in negative symptoms at baseline (p=0.317), post treatment at 9 months follow-up (p=0.169) or at 18 months follow-up (p=0.086). |
| Nechmad 200364 | Israel | Cross-sectional, (5) | 50 | 17.0**±**2.1 | 64 | DSM-IV / SANS | Individuals with schizophrenia and OCD scored higher on the SANS subscale for affective flattening or blunting than those without OCD (p=0.003). No overall differences in negative symptoms (p=0.35). |
| Oades 200665 | Germany | Longitudinal, (5) | 28 | 17.5**±**0.4 | 75 | DSM-IV / SANS | The amplitude event-related brain response mismatch negativity was associated with negative symptoms. |
| Paillere-Martinot 200066 | France | Longitudinal, (5) | 36 | 17.5**±**1.8 (14-21) | 50 | DSM-III-R / SANS | Negative symptoms were higher in individuals with depression (p=0.006) at baseline than in non-affective psychosis. Individuals who developed schizophrenia had more residual negative symptoms at discharge than those with affective psychosis (p=0.03). |
| Pandina 200067 | Multi-country | Other intervention study, (4) | 324 | 15.4**±**1.4 (12-17) | 62.7 | DSM-IV / PANSS | Correlations between speed of processing and negative symptoms at baseline (r=0.309, p<0.05) and 6 months follow up (r=0.184, p<0.05). |
| Parellada 200668 | Spain | Other intervention study, (3) | 50 | 16 (<18) | N.a. | DSM-IV / PANSS | No differences were found between quetiapine and olanzapine in negative symptoms (p>0.05). There was a significant decrease in negative symptoms in both groups (p<0.05). |
| Parellada 201569 | Spain | Longitudinal, (7) | 83 | 15.5**±**1.8 (9-17) | 69 | DSM-IV (KSADS) / PANSS | Primary negative symptoms at 2 years are more prominent in EOP individuals with an initial diagnosis of schizophrenia (compared with BD p=0.002 and other psychosis p=0.003). Primary negative symptoms at 2 years are more prominent in EOP individuals with lower baseline general symptoms (r=-0.242, p=0.043) and more prominent negative symptoms at baseline (p=0.025). |
| Paruk 201770 | South Africa | Cross-sectional, (5) | 45 | 15.9**±**1.8 (10-18) | 68.9 | DSM-IV-TR / PANSS | No significant association between negative symptoms and a family history of psychosis was found (p>0.05). |
| Pencer 200571 | Canada | Longitudinal, (5) | 69 | 17.3**±**1.2 (15-19) | 71 | DSM-IV / PANSS | After two years, 51.0% EOP were in remission from negative symptoms. Negative symptoms were significant predictors of quality of life (p<0.001). |
| Perez-Garza 201672 | Mexico | Longitudinal, (4) | 87 | 14.9**±**1.5 (12-17) | 69 | DSM-IV / PANSS | There was a significant improvement in negative symptoms at 3 and 6 months follow up (𝑝<0.001) but no gender effect (p>0.05). |
| Petruzzelli 201873 | Italy | Cross-sectional, (5) | 60 | <18 | 61.7 | DSM-IV-TR / PANSS, SANS | The four factors model we presented highlights “negative symptoms” as the most consistent factor (blunted affect (N1), emotional withdrawal (N2), lack of spontaneity and flow conversation (N6), active social avoidance (G16), poor rapport (N3), passive/apathetic social withdrawal (N4). |
| Poyurovsky 200874 | Israel | Cross-sectional, (6) | 44 | 16.6**±**1.6 (13-18) | 56.8 | SCID DSM-IV / SANS | No association between OCD symptoms and negative symptoms were found (all p>0.05) |
| Puig 201275 | Spain | Cross-sectional, (5) | 45 | 16.9**±**1.5 (12-18) | 48.9 | DSM-IV-TR / PANSS | Correlations between negative symptoms and daily living skills/ functioning were found (r=-0.348 p<0.05). |
| Ramanathan 201576 | USA | Cross-sectional, (6) | 58 | 13.7**±**2.4 (10-18) | 50 | SCID-DSM-IV / SIPS/SOPS | There was a statistically significant association between negative symptoms in males and a delayed age of puberty (p=0.001) as compared to early maturers. |
| Rapado-Castro 201077 | Spain | Longitudinal, (5) | 99 | 15.5**±**1.8 (7-17) | 66.7 | DSM-IV / PANSS | Negative dimension was the most consistent and stable over time and was predominant at baseline (23.9%) and at 4 weeks (25.7%). |
| Rapado-Castro 201978 | Spain | RCT, (6, high risk of bias) | 22 | 16.3**±**1.2 (14-18) | 59 | DSM-IV-TR / PANSS | An association was found between improvements in executive functioning performance and a reduction in negative symptoms (r=0.758, p=0.029 for semantic; r=–0,733, p=0.025 for verbal fluency). Negative correlations were found between increased verbal fluency (r=-0.73, p=0.025) and a decrease in negative symptoms in the psychoeducation group. |
| Reddy 199679 | South India | Cross-sectional, (2) | 43 | 15**±**1.4 (10-16) | 39.5 | ICD-9/10 / ICD-10 DCR | Negative symptoms appeared in 46.5% EOP individuals with schizophrenia. |
| Reig 201180 | Spain | Longitudinal, (7) | 92 | 15.7**±**1.7 (9-18) | 69.6 | DSM-IV (KSADS-PL) / PANSS | In male individuals, the correlation analysis revealed a significant negative relationship between negative symptom and whole-brain GM volume (r=0.292, p=0.025). In the region of interest analyses of GM volumes, this correlation was significant only in the parietal lobe (right: r=0.399, p=0.002; left: r=0.296, p=0.023). |
| Remberk 201281 | Poland | Cross-sectional, (4) | 32 | 16.7**±**1.5 (13-18) | 46.9 | ICD-10 / PANSS | Negative symptoms correlated with perseverative errors (r=0.31, p<0.05), phonological fluency (r=−0.27, p<0.05) and number of uncommon responses (r=0.27, p<0.05). |
| Remberk 201282 | Poland | Cross-sectional, (6) | 104 | 16.7**±**1.2 (13.4-19.1) | 47.1 | ICD-10 / PANSS | A correlation was found between negative symptoms and length of hospitalization (r=0,194, p=0.004). In schizophrenia more negative symptoms then in acute and transient psychotic disorders were detected (p=0.006). |
| Remberk 201583 | Poland | Longitudinal, (4) | 63 | 16.6**±**1.2 (14.1-19.1) | 50.8 | ICD-10 / PANSS | Negative symptoms were related to mental health service utilization during the follow-up. Severity of negative symptoms was associated with diagnosis of schizophrenia at baseline (β=0.287, p=0.007). A higher level of negative symptoms was associated with a higher probability of receiving pharmacotherapy (β=0.243, p=0.025). The drug-free subgroup with no occupational/educational activity compared with the drug-treated subjects showed lower levels of baseline negative symptomatology (p<0.05). |
| Ross 201384 | USA | Other intervention study, (3) | 19 | 10.5**±**2.4 (6-15) | 73.7 | DSM-IV / SANSS | Negative symptoms improved in EOP individuals on olanzapine in this open label trial after a year (p=0.004). |
| Salazar de Pablo 202185 | Spain | Longitudinal, (5) | 108 | 15.5**±**1.8 (7-17) | 68.5 | DSM-IV / PANSS | Negative symptoms were more severe in EOP with non-affective psychosis than affective psychosis (p=0.045). |
| Savitz 201586 | Multi-country | RCT, (7, low risk of bias) | 174 | 15.3**±**1.5 (12-17) | 66 | DSM-IV / PANSS | No difference found in efficacy for negative symptoms between paliperidone and aripiprazole after two months (p=0.535) or six months (p=0.696). |
| Schwartz-Stav 200687 | Israel | Cross-sectional, (4) | 32 | 17.5 (13-19) | 62.5 | K-SADS-DSMIV / PANSS | A correlation was found between negative symptoms and general unawareness (r=0.48) but not to unawareness for psychotic symptoms (p>0.05). |
| Shaw 200688 | USA | RCT, (5, unclear risk of bias) | 25 | 12.3**±**2.4 (7-16) | 60 | DSM-IV / SANS | Clozapine was more efficacious than olanzapine for negative symptoms (p=0.04; ES=0.89) after eight weeks. |
| Şimşek 201689 | Turkey | Cross-sectional, (4) | 30 | 14.7**±**1.9 (10-17) | 39 | K-SADS-PL / PANSS | There was a significant correlation between decreased IL-10 and increased IL-4 levels with increased negative symptoms (r=-0.65, p=0.02 and r=0.67, p=0.02, respectively). |
| Slosarczyk 202290 | Poland | Longitudinal, (5) | 69 | 16 (14-19) | 49.3 | DSM-IV-TR / N.a. | Premorbid sadness was associated to higher severity of negative symptoms at baseline (p<0.05). Poor emotional expression primarily correlated with later apathy/abulia (p<0.05). |
| Tang 201291 | China | Longitudinal, (5) | 29 | 16.1**±**0.9 (12-19) | 44.8 | DSM-IV-TR / PANSS | The loss of grey matter volume did not correlate with negative symptoms (p>0.05). |
| Thaden 200692 | USA | Cross-sectional, (6) | 59 | 16**±**2.1 (7-18) | 59.3 | DSM-IV / SANS | No significant correlation was found between attentional capacity and negative symptoms (p>0.05). |
| Thakur 200393 | India | Cross-sectional, (7) | 101 | 16.1**±**1.7 (6-18) | 66.3 | DSM-IV / SANS | From four factors generated, two of them focused on negative symptoms: primary negative factor including unchanging facial expression, decreased spontaneous movements, paucity of expressive gestures, poor eye contact, poverty of speech, grooming and hygiene and impersistence) and secondary negative factor (affective non-responsivity, inappropriate affect, lack of vocal inflections, physical anergia, reduced recreational interest and activities, decreased ability to feel intimacy and closeness, poor interpersonal relationships). Individuals in the primary negative group having poor educational background (p=0.002) and individuals in the secondary negative group showed longer illness duration (p<0.001). |
| Vines 202294 | USA | Longitudinal, (5) | 13 | 17.8**±**2.8 (12-25) | 48.9 | SCID-DSM-IV, SIPS/SOPS / SIPS/SOPS | Greater negative symptom severity was associated with less cognitive reappraisal (β=0.27, p=0.02) and greater overall emotion regulation impairment (β=0. 31, p=0.02). |
| Vyas 200795 | UK | Longitudinal, (3) | 40 | 15.6**±**2.3 | 50 | DSM-IV / PANSS | Psychosocial outcome as per the Social Adaptation Self-Evaluation Scale correlated negatively with negative symptoms (r=0.45, p=0.04). Functioning scores did not correlate with negative symptoms (p=0.17). |
| Wang 201796 | China | Longitudinal, (5) | 35 | 15.5**±**1.8 (12-18) | 57.1 | DSM-IV-TR / PANSS | The precuneus with reduced global functional connectivity density is significantly negatively correlated with negative symptoms in the slow-4 band (p<0.05) |
| Wang 202097 | China | Cross-sectional, (6) | 39 | 15.5**±**1.8 (12-18) | 57.1 | DSM-IV-TR / PANSS | The intrinsic functional connectivity and structural properties of the left frontal white matter correlated with negative symptoms in EOP (p<0.05). Negative symptoms were negatively correlated with reduced fiber counts through the frontal white matter (r=-0.39, p=0.043). |
| Wedervang-Resell 202098 | Norway | Cross-sectional, (4) | 39 | 16.3**±**1.4 (12-18) | 66.7 | KSADS-PL / PANSS | Compared with the mild negative group (PANSS Neg <21), the Severe Negative group (p ≥21) had significantly longer DUP (p=0.001) and decreased C-GAS scores (p=0.03). The levels of triglycerides were significantly higher in the severe negative than in the mild negative individual group (p=0.032). |
| Wen 201199 | China | Cross-sectional, (5) | 29 | 14.9**±**1.6 (<18) | 34.5 | DSM-5 / PANSS | Negative symptoms were less severe in EOP than in CHR-P individuals fulfilling DSM-5-APS criteria (p=0.0002). Gray matter volume of the hippocampus was negatively correlated with negative symptoms in EOP (r=-0.474, p=0.001) |
| Wozniak 2008100 | USA | Longitudinal, (3) | 36 | 14.6**±**1.9 (10-17) | 64 | DSM-IV / PANSS | Baseline IQ was correlated with negative (r=-0.706, p=0.007), symptoms at follow-up. No correlation between IQ and negative symptoms (r=-0.212, p=0.228) at baseline. |
| Yang 2014101 | China | Cross-sectional, (5) | 26 | 14.5**±**1.9 (7.5-17.9) | 50 | DSM-IV / PANSS | EOP individuals with more predominant negative symptoms are associated with abnormality in the superior temporal gyri-inferior frontal gyri network (p<0.05.) |
| Zakowicz 2022102 | Poland | Longitudinal, (5) | 31 | 14**±**1.9 (11-18) | 48.4 | DSM-IV / PANSS | Evaluating the correlation between language Embodiment and negative symptoms, a strong correlation was observed between negative symptoms and the "Thought, Language, and Communication Scale" (TLCS (r=0.63, p<0.01) but not Zabór Verbal Task (ZBT, p<0.05). |
| Zheng 2016103 | China | Longitudinal, (4) | 35 | 15.5**±**1.6 (12-18) | 57.1 | DSM-IV-TR / PANSS | Voxel-wise amplitude of low-frequency (0.01–0.08 Hz) fluctuations in the precuneus had a significant negative correlation with PANSS negative symptom scores (r=-0.44, p=0.0067). |
| Zhou 2022104 | China | Cross-sectional, (5) | 20 | (13-18) | 35 | DSM-IV / PANSS | Whole-brain correlation analysis found that the degree centrality in the right superior parietal lobe (SPL) was positively correlated with PANSS-negative symptom scores (r=0.79); degree centrality in the left precuneus was positively correlated with self-certainty) scores (r=0.70); and degree centrality in the left medial frontal gyrus was negatively correlated with self-reflectiveness (scores (r=0.69). |
| APS: Attenuated Psychosis Syndrome; BD: Bipolar Disorder; BPRS: Brief Psychiatric Rating Scale; CBT: Cognitive behavioural therapy; C-GAS: Children's Global Assessment Scale; CSF: Cerebrospinal Fluid; DSM: Diagnostic and Statistical Manual of Mental Disorders; EOP: early onset psychosis; ES: effect size; GAF: global assessment of functioning; GM: gray matter; HR: hazard ration; ICD: International Classification of Diseases; IL: interleukin; IQ: Intelligence quotient; K-SADS-PL: Kiddie Schedule for Affective Disorders and Schizophrenia – Present and lifetime; OR: odds ratio; N.a. no available; NLP: nature language processing; NOS: not otherwise specified; OCD: obsessive compulsive disorder; OPCRIT: Operational Criteria Checklist for Psychotic Illness and Affective Illness; PANSS: Positive and Negative Syndrome Scale; RCT: Randomised Clinical Trial; SANS: Scale for the Assessment of Negative Symptoms; SCID: Structured Clinical Interview for DSM Disorders; SIPS: Structured Interview of Psychosis-risk Syndromes; SOPS: Scale of Prodromal Symptoms; TAU: treatment as usual; WCST: Wisconsin Card Sorting Test. | | | | | | | |

**eTable8**. **Characteristics of included studies (samples with CHR-P individuals)**.

| **First author** | **Country** | **Study design (NOS score, RoB score- if applicable-)** | **Sample size CHR-P** | **Mean age±SD, (range), years** | **Males, %** | **Instruments used (EOP/ Negative symptoms)** | **Key findings** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Addington 2014105 | Multi-country | Cross-sectional, (6) | 155 | 17.8**±**3.7 (13-35) | 52.3 | SIPS/SOPS / SIPS/SOPS | A correlation between depressive symptoms and negative symptoms was found (r=0.38, p<0.01). |
| Amminger 2010106 | Austria | RCT, (7, low risk of bias) | 81 | 16.4**±**2 (13-25) | 33.5 | DSM-IV / PANSS | The omega-3 group had significantly lower negative symptoms scores at 12 weeks (p<0.05), 6 months (p<0.05), and 12 months (r=0.52, p<0.05) than the control cohort. |
| Amminger 2015107 | Austria | RCT, (5, low risk of bias) | 80 | 16.4**±**2.1 (13-25) | 32.5 | PANSS / PANSS | More severe baseline negative symptoms were associated with treatment response in the ω-3 supplemented group compared to the control group (Cohen’s d=0.7) |
| Armando 2012108 | Italy | Cross-sectional, (7) | 111 | 16.6**±**1.5 | 36.9 | PANSS / PANSS | There was a significant group difference in the PANSS negative subscale (p=0.0081), with higher scores in CHR-P individuals with 22q11 compared to those without it. After controlling for the influence of IQ and depressive symptoms, differences remained (p=0.015, p=0.034). |
| Bartholomeusz 2014109 | Austria | Cross-sectional, (4) | 39 | 16.4**±**2.6 (13-25) | 35.89 | PANSS / PANSS | A correlation was found between increased left amygdala volume and negative symptoms in females (p=0.020) but not males. |
| Boldrini 2020110 | Italy | Cross-sectional, (4) | 26 | 15.5**±**1.4 | 46.2 | SIPS/SOPS / SIPS/SOPS | A positive correlation was found between psychotic-level defences and negative symptoms including social anhedonia (r=0.630; p<0.01), avolition (r=0.504; p<0.01), expression of emotions (r=0.510; p<0.01), and experience of emotion and self (r=0.500; p<0.01). |
| Gerstenberg 2020111 | Germany | Cross-sectional, (4) | 21 | 15.0**±**1.4 (12-17) | 47.6 | DSM-IV / SIPS/SOPS | Poorer current global functioning (r=−0.26; p=0.015)., social functioning (r=−0.38, p=0.0007) and role functioning (r=−0.25; p=0.025) were associated with more severe negative symptoms. |
| Giordano 2022112 | Italy | Longitudinal, (6) | 71 | 13.9**±**2.1 (9-17.6) | 59.1 | SIPS/SOPS / SIPS/SOPS | 100% CHR-P experienced negative symptoms of at least moderate severity. Negative symptoms at baseline did not predict transition to psychosis (p=0.76). |
| Lencz 2004113 | USA | Cross-sectional, (5) | 42 | 16.3**±**2.3 | 63.4 | SIPS/SOPS / SIPS/SOPS | No differences in negative symptoms found between at risk individuals with attenuated negative/disorganized symptoms only, CHR-P subjects with attenuated positive symptoms and subjects with schizophrenia-like psychosis (p>0.05). |
| Lindgren 2010114 | Finland | Cross-sectional, (5) | 62 | 16.6**±**0.9 (14-19) | 21 | SIPS/SOPS / SIPS/SOPS | Negative symptoms correlated negatively with processing speed (r=−0.31, p=.014) and verbal performance (r=−0.37, p=0.03). |
| Lindgren 2021115 | Finland | Longitudinal, (6) | 50 | 16.5 (15-18) | 21.6 | SIPS/SOPS / SIPS/SOPS | Negative symptoms predicted transition to psychosis (AUC=0.74, p<0.01). |
| McGorry 2013116 | Austria | RCT, (7, unclear risk of bias) | 115 | 17.9**±** (14-30) | 39.4 | CAARMS / SANS | No significant differences in negative symptoms between the CBT+ risperidone, CBT+ placebo, supportive therapy+placebo and monitoring groups (p>0.05). |
| Miklowitz 2014117 | Multi-country | RCT, (6, high risk of bias) | 129 | 17.4**±**4.1 (12-35) | 57.4 | SIPS/SOPS / SIPS/SOPS | Family-Focused Treatment was not associated to an improvement in negative symptoms (p>0.05). CHR-P individuals who entered the trial on antipsychotics showed greater improvement in total negative symptom scores than those not on antipsychotics (p=0.03). The improvements in total negative symptom scores were not attributable to changes in specific negative symptom items (p=0.90). |
| Niendam 2006118 | USA | Longitudinal, (5) | 45 | 17.7**±**4.0 (12-19) | 64 | SIPS/SOPS / SIPS/SOPS | More severe negative symptoms were associated with poorer social functioning (r=0.47, p=0.001). No correlation between negative symptom score and neurocognitive measures was found (p>0.05). |
| O’Brien 2006119 | USA | Longitudinal, (3) | 26 | 16.2 (12-35) | 53.8 | SIPS/SOPS / SIPS/SOPS | The largest number of critical comments (39%) from the family referred to negative symptoms, particularly social withdrawal (7%) and lack of motivation (32%). 89% of the sample either improved or remained the same on the negative symptom scale. |
| O’Brien 2008120 | USA | Cross-sectional, (3) | 32 | 15.7 (12-35) | 60 | DSM-IV / SIPS/SOPS | Positive remarks offered by family members predict a decrease in negative symptoms (p<0.05). |
| Pelizza 2018121 | Italy | Longitudinal, (5) | 36 | 15**±**1.4 (13-18) | 50 | CAARMS / PANSS, CAARMS | No significant differences found between CHR-P and EOP individuals in negative symptoms including observed blunted affect, alogia and anhedonia (all p>0.05). |
| Pelizza 2020a122 | Italy | Longitudinal, (6) | 90 | 15.9**±**1.6 (13-18) | 54.4 | CAARMS/ PANSS, CAARMS | Difficulties in metacognition- cognition related to cognitive impairments- had significant positive correlations with negative symptoms dimensions (p=0.0001). |
| Pelizza 2020b123 | Italy | Longitudinal, (5) | 76 | 15.8**±**1.6 (13-18) | 52.6 | CAARMS / PANSS, CAARMS | CAARMS anhedonia measure showed significant correlations with negative symptoms (p<0.001). |
| Pitzianti 2019124 | Italy | Cross-sectional, (3) | 25 | 14.8**±**2 (7-18) | 68 | SIPS/SOPS / SIPS/SOPS | A significant correlation between total speed of timed activities and negative symptoms in CHR-P individuals (p=0.038). No correlation between overflow movements (p=0.718) and dysrhythmia (p=0.221) with negative symptoms was found. |
| Quijada 2010125 | Spain | Cross-sectional, (5) | 20 | 15.8 (12-20) | 60 | SIPS/SOPS, PANSS/ SIPS/SOPS, PANSS | 80% CHR-P experienced a reduction of motivation and poor work and school performance, 70% experienced a decrease in the ability to maintain or start social relationships and 55% social withdrawal. |
| Quijada 2012126 | Spain | Longitudinal, (4) | 31 | 15.7**±**3.1 (12-25) | 74 | SIPS/SOPS, PANSS/ SIPS/SOPS, PANSS | 71% improved in negative symptoms. No correlations between attachment (secure, preoccupied, fearful, dismissing) and negative symptoms were found (all p>0.05). |
| Rodriguez-Pascual 2021127 | Spain | Cross-sectional, (6) | 89 | 15.1**±**1.8 (8-17) | 40.7 | SIPS/SOPS/ PANSS | Significant differences in the presence of negative symptoms found between those with and without MDD (90.3% vs 68.2%, p=0.021). A correlation between negative symptoms and depressive symptoms was found (r=0.533, p<0.001). |
| Salazar de Pablo 2020128 | United States | Cross-sectional, (5) | 65 | 15.5**±**1.3 (12-17) | 24.6 | SIPS/SOPS, DSM-5/ SIPS/SOPS | Negative symptoms were significantly correlated with lower current functioning (r=−0.17; p=0.031), lower lowest functioning in the past year (r=−0.20; p=0.014) and lower highest functioning reached in the past year (r=−0.19; p=0.022). Illness severity was associated with negative symptoms (r=−039, p>0.001). |
| Schneider 2019129 | Multi-country | Longitudinal, (4) | 30 | 15.7**±**4.7 (8-33) | N.a. | SIPS/SOPS/ SIPS/SOPS | 66.7% CHR-P individuals had at least one negative symptoms. |
| Shetty 2021130 | Australia | Cross-sectional, (6) | 81 | 17.7**±**3.1 (15-29) | 38.3 | CAARMS/ SANS | Greater preference for eveningness was significantly associated with increased negative symptoms (p=0.02). |
| Spada 2016131 | Italy | Longitudinal, (5) | 22 | 16.1**±**1.2 (12-18) | 54.5 | CAARMS/ CAARMS | 77.3% CHR-P individuals had negative symptoms. 100% CHR-P individuals who transitioned to psychosis had negative symptoms (26.7 % of the total sample after a year). |
| White 2008132 | USA | Longitudinal, (4) | 68 | 17.3**±**3.8 (12-35) | 72 | SIPS/SOPS, SCID-DSM-IV/ SIPS/SOPS | Males were rated as having more severe negative symptoms than females at baseline, 6 months and 12 months follow-up (p<0.05). There was also a significant relationship between average negative symptoms and average global functioning (r=−0.75, p<0.001). |
| Zhang 2021133 | China | Longitudinal, (6) | 244 | 15.8**±**1.3 | 45.9 | SIPS/SOPS/ SIPS/SOPS | Negative symptoms were more severe in adolescents than adults (p<0.001). The conversion outcome was best predicted by negative symptoms compared to other clinical variables (p=0.006, d=0.46). |
|  |  |  |  |  |  |  |  |
| Akouri-Shan 2021134 | USA | Cross-sectional, (3) | 33 | 17.8**±**3.4 (12-23) | 40 | SIPS/SOPS/ SIPS/SOPS | Salience Attribution Test, including adaptive salience attribution did not correlate with negative symptoms (p> 0.05). Greater negative symptoms correlated with poorer social (r=0.7) and role functioning (r=0.5). |
| Mensi 2021135 | Italy | Longitudinal, (5) | 110 EOP | 15.5 (12-17) | 37.3 | DSM-5 | 74.3% of DSM-5 APS individuals reported negative symptoms. |
| 31 CHR-P | 14.5 (12-17) | 48.4 | CAARMS | 93.5% of EOP individuals reported negative symptoms. |
| Pihet 2013136 | Switzerland | Longitudinal, (4) | 28 | 15.6**±**1.3 (13-17) | 68.4 | DSM-IV, SIPS/ SOPS/ PANSS | Individuals who presented more severe negative symptoms at baseline had a significantly lower average treatment motivation (p<0.05). |
| Thomson 2019137 | UK | Longitudinal, (5) | 141 | 16.1**±**1.3 (13-18) | 56.7 | N.a./ PANSS | Including both CHR-P and EOP, negative symptoms improved at 12 months follow-up (p=0.002, d=0.46). Duration of untreated illness did not predict negative symptoms (p=0.07). Early negative symptoms predicter negative symptoms at 12 months follow up (r=0.62). |
| APS: attenuated psychosis syndrome CAARMS: Comprehensive Assessment of AT Risk Mental States; CBT: Cognitive Behavioural Therapy; CHR-P: Clinical High-Risk for Psychosis; DSM: Diagnostic and Statistical Manual of Mental Disorders; EOP: early onset psychosis ICD: International Classification of Diseases; IQ: Intelligence quotient; MDD: major depressive Disiroder; N.a. no available; PANSS: Positive and Negative Syndrome Scale; RCT: Randomised Clinical Trial; SANS: Scale for the Assessment of Negative Symptoms; RoB: risk of bias tool; SCID: Structured Clinical Interview for DSM Disorders; SIPS Structured Interview of Psychosis-risk Syndromes; SOPS Scale of Prodromal Symptoms; TAU: treatment as usual. | | | | | | | |

**eTable9. Publication bias: Egger’s test.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Intercept | SE | Z value | df | P value |
| Total | -1.66 | 1.953 | -0.85 | 19 | 0.3949 |
| EOP | -1.49 | 2.673 | -0.56 | 14 | 0.5780 |
| CHR-P | -2.65 | 1.393 | -1.90 | 5 | 0.0571 |

Df: degrees of freedom; SE: standard error.

**eFig1. Publication bias: funnel plot EOP and CHR-P.**



EOP: Early-onset psychosis; CHR-P: Clinical High-Risk for Psychosis.

**eFig2. Publication bias: funnel plot EOP.**

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EOP: Early-onset psychosis.

**eFig3. Publication bias: funnel plot CHR-P.**

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CHR-P: Clinical High-Risk for Psychosis.

**eMethods1. Search terms.**

We performed a multi-step literature search using the following keywords: (“child\*” OR “adolesc\*” OR “paediatric” OR “pediatric” OR “teen” OR “early-onset” OR “EOP”) AND (“psychosis” OR “schizophrenia” OR “schizoaffective” OR “prodrom\*” OR “ultra-high risk” OR “clinical high risk” OR “clinical high-risk” OR “attenuat\*” OR “APS” OR “high risk” OR “high-risk” OR “BLIPS” OR “brief limited” OR “brief intermittent” OR “genetic high risk” OR “genetic high-risk” OR “GRD” OR “at risk mental state” OR “at-risk mental state” OR “risk of progression” OR “progression to first-episode” OR “basic symptoms”) AND “negative symptoms”.

**eMethods2. Summary of included variables**

Summary of variables extracted included the following information: author and year of publication, country, study design (original or abstract; cross-sectional, longitudinal, randomised clinical trial, other intervention trial), study quality, sample size, age (mean age, SD and range), sex (% of males), diagnostic assessment/ instrument used, method used to assess negative symptoms, primary diagnosis (including % with schizophrenia), % individuals with negative symptoms, treatments received (including % antipsychotics), and key diagnostic, prognostic and therapeutic findings.

**eMethods3. Risk of bias (quality) assessment with Cochrane Risk of Bias tool for randomized clinical trials**

The Cochrane Risk of Bias tool138 was used to assess and classify the risk of bias in each of the included studies.

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 unclear risk of bias 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 bias139.

**eResults1. Diagnostic categories and subgroups and negative symptoms in EOP.**

Negative symptoms seem to be more frequent in EOP individuals with a diagnosis of schizophrenia than with other psychosis in hospitalized individuals (p=0.04).24 Individuals with stable schizophrenia-spectrum disorder in the community seem to also have more severe negative symptoms than those with stable affective psychotic disorders (p<0.01).39 Further, negative symptoms were more severe in EOP with non-affective psychosis than affective psychosis (p=0.045)128 according to one of the studies. Specifically, in another study, individuals with schizophrenia (72%) and schizoaffective disorder (43%) had more negative symptoms at baseline than those with bipolar disorder (21%) or psychosis-NOS (9%).53 More severe negative symptoms were found in schizophrenia than in acute and transient psychotic disorders (p=0.006).82 Within schizophrenia, a trend toward higher negative symptom scores was found in the undifferentiated schizophrenia group compared to the paranoid schizophrenia group (p=0.05).8 In regards to other EOP subgroups, brief psychotic disorder was associated with lower maximum levels of negative symptoms compared to psychosis NOS (p=0.02).17

**eResults2. Neuroanatomical and neuroimaging and other neurobiological non-cognitive findings and negative symptoms in EOP.**

Altogether, 15 (15%) studies focused primarily on neuroanatomical and neuroimaging findings. A correlation between negative symptoms and smaller total cerebral volume was found (r=-0.65, p<0.001),5 although not consistently.52 Significant negative correlations between the bilateral hippocampal volumes and total negative symptoms (p<0.025) were also found.23 Grey matter volume of the hippocampus was negatively correlated with negative symptoms in EOP (r=-0.474, p=0.001).99 Negative symptoms were negatively correlated with reduced fiber counts through the frontal white matter (r=-0.39, p=0.043).97 EOP individuals with more predominant negative symptoms had more abnormalities in the superior temporal gyri-inferior frontal gyri network (p<0.05).101 Voxel-wise amplitude of low-frequency (0.01–0.08 Hz) fluctuations in the precuneus had a significant negative correlation with PANSS negative symptom scores (r=-0.44, p=0.0067).103 Whole-brain correlation analysis found that the degree of centrality in the right superior parietal lobe was positively correlated with PANSS-negative symptom scores (r=0.79).104The precuneus with reduced global functional connectivity density was significantly negatively correlated with negative symptoms in the slow-4 band (p<0.05).96 There was a significant correlation between decreased IL-10 and increased IL-4 levels with increased negative symptoms (r=-0.65, p=0.02 and r=0.67, p=0.02, respectively).89 The loss of grey matter volume did not correlate with negative symptoms (p<0.05).91 Triglyceride levels were significantly higher in the severe negative group than in the mild negative individual group (p=0.032).98

A negative correlation was found between negative symptoms and the abnormal dynamic amplitude of low-frequency fluctuations (dALFF) variability of the right middle temporal gyrus (r=-0.2723, p=0.0207).50 The risk allele A of ZNF804A was associated with greater severity of negative symptoms in EOP (p<0.05).6 The Val/Val group had a higher negative symptom score compared to the Val/Met group (p=0.018, Cohen’s d=0.55).42 No association found between negative symptoms and sleep spindle density (p=0.07).32

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