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NEGATIVE SYMPTOMS IN CHILDREN AND ADOLESCENTS WITH EARLY-ONSET PSYCHOSIS AND AT CLINICAL HIGH-RISK FOR PSYCHOSIS: SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background: Early-onset psychosis (EOP) refers to the development of a first episode of psychosis before 18 years. Individuals at clinical high-risk for psychosis (CHR-P) include adolescents and young adults, although most evidence has focused on adults. Negative symptoms are important prognostic indicators for patients with psychosis. However, research focusing on children and adolescents (C&A) is limited.

Aims: Provide meta-analytical evidence and a comprehensive review of the status and advances in the diagnosis, prognosis and treatment of negative symptoms in C&A with EOP & CHR-P.

Method: PRISMA/MOOSE-compliant systematic review (PROSPERO:CRD42022360925) from inception through 18-08-2022, in any language, to identify individual studies conducted in EOP/CHR-P C&A (mean age <18 years) providing findings on negative symptoms. Findings were systematically appraised. Random-effects meta-analyses were performed on the prevalence of negative symptoms in EOP/CHR-P C&A, carrying out sensitivity analyses, heterogeneity analyses, publication bias assessment and quality assessment using the Newcastle-Ottawa Scale.

Results: Of 3,289 articles, 133 were included (n=6,776 EOP, mean age=15.3±1.6 years, males=56.1%; n=2,138 CHR-P, mean age=16.1±1.0 years, males=48.6%). There were negative symptoms in 60.8% (95%CI=46.4%–75.2%) of C&A with EOP and 79.6% (95%CI=66.3%–92.9%) of C&A at CHR-P. Prevalence and severity of negative symptoms were associated with poor clinical, functional and intervention outcomes in the included studies on CHR-P&EOP. Different interventions were piloted with variable results requiring further replication.

Conclusions: Negative symptoms are common in C&A at early stages of psychosis, particularly in those at CHR-P, and associated with poor outcomes. Future intervention research is required so that evidence-based treatments will become available for C&A.
Relevance statement

This first in field comprehensive review on negative symptoms in children and adolescents is relevant to practising psychiatrists as establishes the following learning points:

- Negative symptoms are at least as common in children and adolescents with early-onset psychosis (EOP) as in adults.
- Negative symptoms frequently appear during the prodromal period and in adolescents at clinical high-risk for psychosis (CHR-P).
- Negative symptoms are associated with poor clinical, functional and intervention outcomes in EOP and CHR-P.
- Pharmacological interventions for negative symptoms in EOP show variable results, warranting further research. Clozapine has the most consistent evidence and could be indicated for treatment-resistant EOP.
INTRODUCTION

Early-onset psychosis (EOP) refers to the development of a first episode of psychosis before the age of 18 years.\(^1\) EOP is characterised by a high frequency of negative symptoms.\(^2\) Negative symptoms are defined as a reduction of normal functions either related to motivation and interest (e.g., avolition, anhedonia, and asociality) or expressive functions (e.g., blunted affect and alogia)\(^9\) and can be evaluated categorically based on their presence/absence or continuously based on their severity. Younger age at onset is associated with more negative symptoms at follow-up,\(^4\) and the severity of negative symptoms is associated with several poor outcomes.\(^5-7\) Still, negative symptoms are challenging to identify in young people,\(^8\) and over 60% of EOP individuals experience “poor” long-term outcomes and unmet therapeutic needs.\(^9\) Furthermore, the prevalence of negative symptoms in EOP and their effect on prognosis remains unclear.\(^6\)

Prior research with clinical high-risk for psychosis (CHR-P) population typically includes adolescents and young adults\(^10\) with different risk groups, including ultra-high risk criteria (eTable1) and basic symptoms criteria (eTable2). However, most of the evidence examining negative symptoms focuses on adult or mixed CHR-P samples, with relatively little research focusing on children and adolescents (C&A).\(^11,12\) However, in C&A at CHR-P, negative symptoms have been found to be clinically relevant and sometimes predominant psychopathologically.\(^13\) In C&A at CHR-P, negative symptoms have also been associated with poor outcomes and poor recovery levels.\(^14\)

To our knowledge, no previous meta-analysis evaluated the prevalence of negative symptoms in C&A with EOP and C&A at CHR-P or investigated the influence of moderating factors, such as sex, age or study design on the prevalence of negative symptoms. From a diagnostic and prognostic perspective, previous systematic reviews and meta-analyses examined the link between negative symptoms and functioning in C&A at CHR-P,\(^15\) the association of cannabis and nicotine use with negative symptoms,\(^16\) the association between the duration of untreated psychosis and negative symptoms,\(^17\) and the relationship between depressive symptoms and negative symptoms.\(^18\) These studies have been limited in scope: they have just examined correlates of negative symptoms or outcomes associated with negative symptoms\(^15-18\); none of these studies focused on C&A; none comprehensively summarized the available evidence or provided methodological and research agenda recommendations to advance the field.

Previous meta-analyses have evaluated the efficacy of antipsychotic medications for the treatment of psychotic symptoms in EOP, finding that most antipsychotics were efficacious for positive symptoms.\(^19-21\) Meta-analytical reports from a much smaller cohort of studies showed
that antipsychotics reduced negative symptom scores compared to placebo, but no comparisons were statistically significant except for clozapine in some studies, highlighting the need for further research on the treatment of negative symptoms. In the CHR-P field, research on therapeutic advances for C&A has been even more limited, and most studies have focused on other outcomes such as transition to psychosis.

Based on the above, the aim of this study was to a) evaluate the prevalence of C&A with EOP and at CHR-P who presented with negative symptoms and which factors increased or decreased this prevalence, and b) provide a comprehensive review of the current status and advances in the diagnosis, prognosis and treatment of negative symptoms in C&A with EOP. Our hypothesis was that the prevalence of negative symptoms would be at least as common in EOP as in adult-onset psychosis and as common in C&A at CHR-P as in C&A with EOP. We further hypothesised that the severity of negative symptoms would be associated with poor outcomes. Finally, we were keen to explore whether evidence for interventions for negative symptoms in both C&A with EOP and C&A at CHR-P was sufficient to recommend specific interventions above others.

METHOD

This systematic review and meta-analysis was registered in PROSPERO (CRD42022360925). It was conducted following the guidelines of the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses” (PRISMA) 2020 statement (eTable3-4) and Moose checklist (eTable5), following EQUATOR Reporting Guidelines.

Search strategy and selection criteria
We performed a multi-step literature search (keywords in eMethods1). First, PubMed and Web of Science database (Clarivate Analytics) were searched, incorporating 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 from inception until 18-08-2022, without language restriction. Second, we searched for data in relevant conference proceedings, including the “Schizophrenia International Research Society” (SIRS) and Early Intervention in Mental Health international conference (IEPA), as well as in trial registries (clinicaltrials.gov, WHO International Clinical Trials Registry Platform (ICTRP)). Following recent guidelines, search terms were simplified for the latest (“early-onset”, “adolescents”, and “negative symptoms”). Third, we completed our search by reviewing the references of systematic reviews/meta-analyses retrieved during our search.
Articles identified were screened as abstracts by independent researchers (GSP, VS), and those that were irrelevant were screened out. The full texts of the remaining articles were assessed for eligibility against the inclusion and exclusion criteria, and decisions were made regarding their final inclusion in the systematic review by consensus or mitigation.

Inclusion criteria for the overall review and synthesis were a) original individual studies, abstracts or conference proceedings, either cross-sectional, longitudinal, randomised clinical trials (RCTs) or other intervention studies, b) providing relevant information/results on negative symptoms in our populations of interest, c) conducted in C&A (mean age <18 years in line with previous reviews on C&A at CHR-P)\(^1\), d) diagnosed with EOP or at CHR-P as per validated instruments and diagnostic criteria (e.g. DSM-any version, ICD-any version and equivalents for EOP, SIPS/SOPS, CAARMS and equivalents\(^2\)\(^8\)\(^9\) for CHR-P), f) published in any language. Exclusion criteria were a) reviews, editorials or clinical cases, b) studies reporting on other mental health conditions or with a mean age ≥18 years old (since no similar review was found for EOP, studies including EOP individuals >25 years were excluded), c) studies reporting only negative symptoms scores (e.g. PANSS scores) without relevant additional results regarding negative symptoms as per established validators, d) studies without results in C&A with EOP or at CHR-P. Overlap was allowed for the systematic review as long as the key findings were not identical. However, for the meta-analysis, an additional inclusion criterion was that of non-overlapping samples (≤50% overlapping sample) as per our protocol.

**Outcome measures, covariates and data extraction**

Independent researchers (BP, JVS, AA) extracted data from all included studies into an Excel spreadsheet. Any discrepancies were resolved through consensus or consulting a senior researcher (GSP) when necessary. The variables extracted can be found in eMethods2.

**Quality assessment**

Quality was assessed using a modified version of the Newcastle-Ottawa Scale (NOS) for cross-sectional and cohort studies. Studies were awarded a maximum of eight points (items can be found in eTable6). Additionally, for RCTs, the “Cochrane Risk of Bias Tool” (RoB2) was used, and the overall quality was rated as low risk of bias, unclear risk of bias, or high risk of bias (see eMethods3).

**Qualitative data synthesis**
We provided a narrative synthesis of the findings from the included studies. The available evidence was structured into diagnostic factors, prognostic factors and therapeutic factors. Evidence was provided separately for C&A with EOP and at CHR-P.

Quantitative meta-analysis

Random-effects meta-analytical estimates were computed independently and categorically for C&A with EOP and at CHR-P, including the prevalence of EOP and CHR-P with negative symptoms as per individual study definition. The meta-analyses were conducted with Stata/MP 16.0 with the metaprop package of STATA statistical software (StataCorp) for Mac, which was developed for pooling proportions in a meta-analysis of multiple studies, and with Comprehensive Meta-analysis V3. The 95% confidence intervals (CI)s were derived from Wilson score procedures. Publication bias was assessed with the metafunnel function of Stata that produces funnel plots for assessing small-study reporting bias in meta-analysis, and with Egger’s test in the metabias function of Stata. Heterogeneity among study point estimates was evaluated with the I² index. Since we expected significant heterogeneity, random-effects models were used.

We conducted sub-analyses and meta-analytical regression analyses to estimate the association between the prevalence of negative symptoms and moderating factors. Sub-analyses included (i) decade of publication (1991-2000, 2001-2010, 2011-2022), (ii) continent (Europe, Asia, North-America, Africa -due to availability of data-), (iii) age (comparing studies including some young adults ≥18 years compared to those with only C&A); (iv) design (cross-sectional, longitudinal). Meta-regression analyses evaluated the influence of the (i) publication year, (ii) % of schizophrenia, (iii) sample size; (iv) mean age, (v) % of males, (vi) % of patients on antipsychotics and (vii) quality of the studies (NOS scores) on the results. Statistical significance was considered when p<0.05.

RESULTS

Our literature search identified 3,289 studies. 3,193 were screened at title and abstract level, and 289 studies were assessed at full text, against inclusion and exclusion criteria. Of those, 133 studies were finally included in the systematic review: 129 (97%) were written in English and 4 (3%) in other languages; 100 (77.5%) focused on EOP, 29 (21.8%) on CHR-P, and 4 (3%) on both (Fig1). Across all studies, 9.055 C&A were included (6,776 with EOP, 2,138 at
CHR-P and 141 without clear designation to one or the other diagnostic group). The sample size of the studies ranged from 10 to 638 (median=45). In total, 68 (48.9%) studies were carried out in Europe, 35 (26.3%) studies in North-America, 24 (18.0%) in Asia, 2 (1.5%) in Australia, 1 (0.8%) in South-America, 1 (0.8%) in Africa, and 2 (1.5%) in more than one continent. Altogether, 127 studies (95.5%) were available as full manuscripts and 6 (4.5%) as abstracts/conference proceedings. Overall, 56 (42.1%) studies were cross-sectional, 52 (39.1%) studies were longitudinal observational studies, 14 (12.0%) were RCTs, and 11 (6.8%) were other intervention studies. The overall mean age of the participants was 15.5±1.6 years, and 54.1% were males. The mean age of C&A with EOP was 15.3±1.6 years, and 56.1% were males. The mean age of C&A at CHR-P was 16.1±1.0 years and 48.6% were males.

**Quality assessment**

Overall, the quality of the studies ranged from 1 to 8 in the included studies, with a median of 5 and a mean of 4.8±1.4. 4 (28.6%) RCTs were rated as low risk of bias, 4 (28.6%) RCTs were rated as unclear risk of bias and 6 (42.9%) RCTs were rated as high risk of bias (eTable7-8). The quality of the studies evaluating C&A with EOP ranged from 1 to 8, with a median of 5 and a mean of 4.7±1.4 (eTable7). The quality of the studies evaluating C&A at CHR-P ranged from 3 to 8, with a median of 5 and a mean of 5.1±1.3 (eTable8).

**Systematic Review in C&A with EOP**

Characteristics of the included studies and key findings related to C&A with EOP can be found in eTable7. Meta-analytical findings evaluated at meta-analytical level will be reported separately below.

**Diagnostic or detection factors**

42 (42.0%) studies focused on diagnostic or detection factors. Findings related to diagnostic categories and subgroups can be found in eResults1, while findings related to neuroanatomical, neuroimaging and other neurobiological non-cognitive findings can be found in eResults2. Findings on clinical factors, functioning and quality of life and cognitive factors are synthesized below:

Altogether, 12 (12.0%) studies focused primarily on co-morbidity and clinical factors. Negative symptoms were more severe in C&A with EOP with higher levels of depression (p=0.023).\(^ {32}\) The prevalence of negative symptoms was associated with enuresis (OR=1.93, p<0.05) and
incontinence during psychosis (OR=3.35, p=0.005) in C&A with EOP. No overall differences in negative symptoms between C&A with EOP with and without OCD were found (p>0.05). A positive association 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). Also, an association was found between more severe negative symptoms and greater emotion regulation impairment (β=0.31, p=0.02). Interestingly, C&A with EOP who never attempted suicide had more negative symptoms during the first episode than those with previous attempts (p<0.05), and the % of history of suicide attempts was higher in those without persistent negative symptoms (p=0.002). There was an association between negative symptoms in males and a delayed age of puberty (p=0.001), which did not appear in females. A family history of psychosis or family burden did not seem to have an effect on negative symptoms (p>0.05).

Altogether, 12 (12.0%) studies focused primarily on functioning and quality of life. In EOP, negative symptoms were associated with impairment in premorbid functioning (p<0.01), global functioning (p<0.01), social functioning (p<0.01), role functioning (p=0.003), daily living skills (r=-0.348, p<0.05), peer relationships (r=0.26, p<0.005), quality of life (p<0.001) and general unawareness (r=0.48), but not to unawareness about psychotic symptoms (p>0.05). Negative symptoms were increased in C&A with EOP with declining social support compared to those with a stable social support group (p<0.05).

Altogether, 7 (7.0%) studies focused primarily on cognitive factors. More negative symptoms were associated with smell identification deficits (r=0.47, p=0.03), lower IQ (r=0.41–0.63, p<0.05) and lower performance on some executive functions and working memory tasks. Specifically, negative symptoms were associated with worse speed of processing at baseline (r=0.309, p<0.05) and six months follow-up (r=0.184, p<0.05), more perseverative errors (r=0.31, p<0.05), less phonological fluency (r=-0.27, p<0.05), higher number of uncommon responses (r=0.27, p<0.05) and slower response time (r=0.44, p=0.015). Additionally, specific negative symptoms were associated with specific cognitive domains. This included the association between apathy (β=-0.257, p=0.002) and diminished expression (β=-0.259, p=0.001) with verbal learning; and between diminished expression and speed of processing (β=-0.173, p=0.024). However, no significant association was found between negative symptoms and attention (p<0.05).

Prognostic factors

Altogether, 37 (37%) studies looked at longitudinal prognostic factors. The key factors about
the changes in negative symptoms in C&A with EOP and the factors that contribute to these changes are reported below following the same order as above (diagnostic categories and subgroups, clinical factors, functioning and quality of life, neurobiological findings and cognitive factors) including additionally prognostic therapeutic factors.

The trajectory of negative symptoms was variable. One study found worsening of negative symptoms after six months,\textsuperscript{57} and three others reported consistent and stable negative symptoms,\textsuperscript{58-60} including after as many as 42 years (p=0.935).\textsuperscript{60}

Patients who developed schizophrenia had more negative symptoms than those diagnosed with affective psychosis one year after their index admission (p=0.03).\textsuperscript{61} Negative symptoms at two years were more prominent in C&A with EOP with lower baseline general symptoms (r=-0.242, p=0.043) and more prominent negative symptoms at baseline (p=0.025).\textsuperscript{62} Duration of untreated psychosis was higher in those with persistent negative symptoms (p=0.022).\textsuperscript{39}

Negative symptoms at baseline was the only significant variable that predicted functional outcome at the two-year follow-up (p=0.010).\textsuperscript{63} Negative symptoms at baseline also predicted lower maximum levels of functioning achieved at one year (β=0.6, p=0.005) and two-year follow-up (β=0.5, p=0.003).\textsuperscript{52,64} Greater improvement in negative symptoms correlated with a thinner frontal cortex at baseline (r=0.5, p=0.003).\textsuperscript{65} There was also an association between left frontal cerebrospinal fluid (CSF) volume increase during follow-up (r=0.58; p=0.003) and left parietal CSF increase (r=0.45; p=0.03) with negative symptoms.\textsuperscript{66} Interestingly, negative symptoms at baseline predicted an improvement in executive performance after two years (β=4.688, p=0.008).\textsuperscript{67} Finally, negative symptoms at admission were predictors of poor treatment efficacy in EOP (OR=0.945, p=0.009).\textsuperscript{68} In fact, negative symptoms were significantly associated with multiple treatment failures (HR=1.62, p=0.02).\textsuperscript{6}

\textit{Therapeutic factors}

Altogether, 37 (37%) studies looked directly or indirectly at therapeutic factors and response to interventions. Participants were not selected based on the presence of negative symptoms. The key advances in pharmacological interventions in RCTs, pharmacological interventions in other clinical trials, psychosocial interventions in RCTs, and psychosocial interventions in other clinical trials are detailed below.

Evidence in EOP coming from RCTs was limited for pharmacological interventions. Clozapine decreased negative symptoms in treatment-resistant EOP compared to haloperidol in a double-blind RCT (p=0.002).\textsuperscript{69} Clozapine was also more efficacious in treatment-resistant EOP reducing negative symptoms than olanzapine after eight weeks (p=0.04; d=0.89).\textsuperscript{70} and
12 weeks (p=0.02, d=0.92)\textsuperscript{71} in another RCT. Treatment with lurasidone was associated with greater improvement versus placebo in negative symptoms for C&A with previously treated EOP (p=0.017; SMD=0.32) but not in treatment-naïve C&A with EOP.\textsuperscript{72} In regards to evidence from other intervention studies, negative symptoms improved after 20 days (p<0.001)\textsuperscript{73} and 88 weeks\textsuperscript{74} in an open-label trial with quetiapine. One study in C&A with EOP found that negative symptoms responded better to aripiprazole than positive symptoms (p=0.028).\textsuperscript{75} In a randomised open-label study comparing olanzapine with risperidone, negative symptoms improved after eight weeks (p<0.01)\textsuperscript{76} and after a year more\textsuperscript{77} and achieved a ≥50% reduction in negative symptoms more frequently with olanzapine (41.7%) than with risperidone (7.7%) (p=0.047) (note this difference disappeared following Bonferroni correction).\textsuperscript{78} However, efficacy was similar for risperidone (14% decline in negative symptoms), olanzapine (17.7% decline), and haloperidol (19.2% decline) in another study.\textsuperscript{79} No differences in negative symptom reduction were found between quetiapine and olanzapine (p>0.05).\textsuperscript{80} Similarly, no difference in efficacy for negative symptoms emerged between paliperidone and aripiprazole after two months (p=0.535) or six months (p=0.696).\textsuperscript{81}

Evidence coming from RCTs was also limited for psychosocial interventions. In one RCT a psychoeducation group for C&A with EOP and their parents showed a greater reduction in negative symptoms than the non-structured group (r=0.41).\textsuperscript{82} However, the improvement did not persist after two years.\textsuperscript{83} There was, though, an association between improvements in executive functioning performance and a reduction in negative symptoms (p<0.05) in the psychoeducation group.\textsuperscript{84} In regards to evidence from other intervention studies, participants attending a programme of residential outpatient care following discharge from a clinic showed a significantly greater decrease in negative symptoms than the control group (p=0.002).\textsuperscript{85} No differences in negative symptom improvement were found between cognitive behavioural therapy added to treatment as usual and treatment as usual only at the end of the intervention (p=0.317), as well as at nine months follow-up (p=0.169) or 18 months follow-up (p=0.086).\textsuperscript{86}

**Systematic Review in C&A at CHR-P**

Characteristics of the included studies and key findings related to CHR-P can be found in eTable8. Meta-analytical findings evaluated at meta-analytical level will be reported separately below.

**Diagnostic or detection factors**

Altogether, 13 (44.8%) studies focused primarily on diagnostic or detection factors. The key diagnostic and detection factors in CHR-P are reported below following the same order as
above (diagnostic categories and subgroups, clinical factors, functioning and quality of life, neurobiological findings and cognitive factors).

More severe negative symptoms were associated with greater illness severity \((r=-0.39, p>0.001)\),\(^{87}\) poorer current global functioning \((r=-0.26; p=0.015)\),\(^{88}\) social functioning \((r=0.38–0.47, p\leq0.001)\)\(^{88,89}\) and role functioning \((r=-0.25; p=0.025)\),\(^{88}\) 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 \((r=-0.19; p=0.022)\).\(^{87}\) A correlation between negative symptoms and depressive symptoms was also observed \((r=0.380–533, p<0.01)\),\(^{90,91}\) particularly anhedonia \((p<0.001)\).\(^{92}\) No correlations between negative symptoms and attachment \((p>0.05)\)\(^{93}\) were found. No differences in negative symptoms were found between C&A with attenuated negative/disorganised symptoms only, C&A at CHR-P with attenuated positive symptoms, and subjects with schizophrenia-like psychosis \((p>0.05)\).\(^{94}\) More patients with negative symptoms were found in C&A at CHR-P with major depressive disorder than without major depressive disorder \((90.3\% \text{ vs } 68.2\%, p=0.021)\).\(^{96}\) 70% of C&A at CHR-P experienced a decrease in the ability to start/maintain social relationships, \(80\%\) experienced poor work and school performance and \(55\%\) experienced social withdrawal.\(^{95}\)

Negative symptoms were more severe in C&A at CHR-P with \(22\text{q}11\) than without a \(22\text{q}11\) diagnosis \((p=0.0081)\).\(^{96}\) From a neuroimaging perspective, larger left amygdala volumes were associated with negative symptoms in females \((p=0.020)\) but not in males.\(^{97}\) Negative symptoms were associated with worse processing speed \((r=-0.31, p=0.014)\) and verbal performance \((r=-0.37, p=0.03)\)\(^{98}\) as well as the total speed of timed activities \((p=0.038)\).\(^{99}\) Moreover, different negative symptom dimensions were associated with difficulties in metacognition (i.e., cognition related to cognitive impairments) \((p<0.001)\).\(^{100}\) However, no significant associations emerged between negative symptoms and neurocognitive measures in another study \((p>0.05)\).\(^{89}\)

**Prognostic and therapeutic factors**

Altogether, 18 (53.1\%) studies focused on longitudinal prognostic or therapeutic factors. The key factors regarding changes in negative symptoms in C&A at CHR-P and the factors that contribute to these changes are reported below following the same order as above (diagnostic categories and subgroups, clinical factors, functioning and quality of life, neurobiological findings and cognitive factors, therapeutic factors). Participants in clinical trials were not selected based on the presence of negative symptoms.
Males had more severe negative symptoms than females at six months and 12 months follow-up (p<0.05). Negative symptoms at baseline did not predict transition to psychosis (p=0.76) in one study (n=71, 1-year follow-up), whereas they did in another one (n=153, 7-year follow-up) (AUC=0.74, p<0.01). In fact, conversion was best predicted by negative symptoms compared to other clinical variables in C&A at CHR-P (p=0.006, d=0.46), and 100% of C&A at CHR-P who transitioned to psychosis had negative symptoms in a further study. Additionally, positive remarks by family members were associated with decreased negative symptoms (p<0.05).

In a RCT, ω-3 fatty acid treatment was associated with significantly lower negative symptom scores at 12 weeks (p<0.05), six months (p<0.05), and 12 months (r=0.52, p<0.05) than placebo. More severe baseline negative symptoms were associated with treatment response in the ω-3 supplemented group compared to the placebo group (d=0.7). However, no significant differences in negative symptoms between the groups receiving CBT& risperidone, CBT& placebo, supportive therapy& placebo, and monitoring only were found in another study (p>0.05). Family-focused treatment was also not associated with an improvement in negative symptoms (p>0.05). Naturalistically, C&A at CHR-P who entered a family-focused treatment trial on antipsychotics showed greater improvement in negative symptoms than those not on antipsychotics (p=0.03).

**Meta-analyses on the prevalence of negative symptoms**

Twenty studies and 1,799 individuals were included in the meta-analysis: 1,457 C&A with EOP (mean age=15.5±1.2 years, 52.1% males) and 342 C&A at CHR-P (mean age=15.2±0.9 years, 52.6% males). Note, this is 15% of the included studies while the rest were not meta-analysed as they evaluated negative symptoms continuously (i.e. their severity) or were overlapping with these studies. Altogether, 66.0% (95%CI=53.6–78.5%) of the total sample had negative symptoms (k=20, n=1,799). Heterogeneity (I²) across the included studies was statistically significant (I²=98.0%, p<0.001). Publication bias was not detected in the funnel plot (eFig1) or Egger’s test (p=0.395) (eTable9). Notably, no overlap was found in any of the studies included in the meta-analysis.

Of the C&A with EOP, 60.8% (95%CI=46.4–75.2%) had negative symptoms (k=15, n=1457) (Fig2). Heterogeneity across the included studies was statistically significant (I²=97.5%, p<0.001). Publication bias was not detected in the funnel plot (eFig2) or Egger’s test (p=0.578) (eTable9). Of the C&A at CHR-P, 79.6% (95%CI=66.3–92.9%) had negative symptoms (k=6, n=342) (Fig3). Heterogeneity across the included studies was statistically significant.
(I²=92.2%, p<0.001). Publication bias was not detected in the funnel plot (eFig3) or Egger’s test (p=0.057) (eTable9).

**Sub-analyses and meta-regression analyses**

In the sub-analyses, the decade of publication seemed to moderate the prevalence of negative symptoms (Q=10.427, p=0.005). Studies published in 2011-2022 detected negative symptoms in 70.3% (56.6%–81.1%), while studies published in 2001-2020 detected negative symptoms in 66.0% (43.2%–83.2%) and studies published in 1991-2000 detected negative symptoms in 43.6% (34.0%–53.8%) C&A with EOP or at CHR–P.

The continent of publication also moderated the prevalence of negative symptoms (Q=9.145, p=0.027). Studies published in Europe (72.6%, 95%CI=59.2%–82.9%) and Asia (60.9%, 95%CI=24.9%–88%) found a higher prevalence of negative symptoms than those published in North-America (49.7%, 95%CI=41.6%–57.8%) or Africa (46.5%, 95%CI=32.3–61.3%).

No differences were found between studies including some individuals ≥18 years compared to those studies including only individuals <18 years (Q=0.026, p=0.871), or between cross-sectional studies and longitudinal studies (Q=0.020, p=0.889) (table1).

In the meta-regression analyses, neither publication year, % of schizophrenia, sample size, mean age, % of males, % of patients on antipsychotics nor NOS scores were significantly associated with the prevalence of negative symptoms (all p>0.05) (table2).

**DISCUSSION**

To the best of our knowledge, this is the first systematic review to provide a comprehensive review evaluation of the evidence regarding negative symptoms and diagnostic, prognostic and therapeutic factors in C&A with EOP or at CHR-P. Additionally, this is the first quantitative meta-analysis on this topic. We systematically reviewed 133 studies evaluating 6,776 C&A with EOP and 2,138 C&A at CHR-P, and provided the first meta-analysis on the prevalence of negative symptoms in C&A in 20 studies and 1,799 individuals, including 1,457 C&A with EOP and 342 at CHR-P, for those studies evaluating the presence/absence of negative symptoms and independent of whether they also reported on the dimensional severity of negative symptoms. The prevalence of negative symptoms found in C&A with EOP was 61%, being 80% the prevalence found in C&A at CHR-P. In general, negative symptoms were associated with poorer clinical, functional, neurobiological, cognitive and intervention
outcomes in both C&A with EOP and C&A at CHR-P individuals, as detailed in the included studies and the systematic review above. Different interventions in heterogenous populations have been piloted with variable results that require further study replication. Overall, these findings suggest that negative symptoms are frequent and clinically relevant both in C&A with EOP and at CHR-P.

One of our main findings is that over 60% of C&A with EOP experience negative symptoms when these are evaluated. Negative symptoms seem to appear in about 30%–50% of individuals with an adult-onset first episode of psychosis. The prevalence observed was thus 20–100% higher in C&A with EOP than in adults. There are different hypotheses or explanations for these results. On the one hand, it may be that this higher prevalence of negative symptoms is due to other characteristics of C&A with EOP, which may in turn be associated with poor prognosis. For instance, C&A with EOP present with more neurodevelopmental difficulties, poorer premorbid adjustment, more cognitive impairment, and higher impulsivity than individuals with adult-onset psychosis. Alternatively, it may be that the participants were particularly enriched in risk factors. Of note, individual studies found that C&A with EOP showed negative symptoms more frequently, and that an earlier age of onset was associated with a higher number of (and more severe) negative symptoms. In any case, the assessment and management of negative symptoms in C&A with EOP should be prioritised. Psychiatrists and other mental health professionals should actively and comprehensively evaluate negative symptoms in young people. This includes CAMHS clinicians treating C&A with EOP who present to their clinic for the first time, and adult clinicians when these patients transition to their services. On a positive note, our sub-analyses suggest that in the last two decades the identification of negative symptoms has improved globally, at least in research studies. Nevertheless, a potential reason for health professionals not focusing on negative symptoms clinically may be rooted in the fact that high-level evidence for specific treatments for negative symptoms is lacking. While in adults with schizophrenia, at least, antidepressants and aerobic exercise have shown to improve negative symptoms, no such trial data exist in C&A with EOP.

Another particularly relevant finding is that negative symptoms appeared in almost 80% of C&A at CHR-P and that this prevalence was higher than for C&A with EOP. Importantly these findings held true at a meta-analytical level. It seems that negative symptoms are observed in the context of emerging attenuated positive symptoms during the prodromal period before the first episode of psychosis. Previous evidence suggests that negative symptoms may be the most common first symptoms of schizophrenia, potentially appearing one year before the emergence of attenuated positive symptoms. This sequence of events has led some
researchers to suggest that individuals with negative symptoms should be included as a new clinical risk group for developing psychosis. However, one prospective cohort study found the conversion rate to psychosis in the group with negative symptoms only was about 5% at 5 years, indicating that negative symptoms alone have limited positive predictive validity. The implication is that screening instruments and CHR-P services should continue identifying ‘high risk’ based on attenuated positive clinical symptoms. To note, clinical services to prevent psychosis do typically focus on (attenuated) positive symptoms in their initial assessment to identify C&A at CHR-P. An alternative explanation for the higher prevalence of negative symptoms in CHR-P could simply be that the instruments used to detect negative symptoms in C&A are more sensitive. To note, negative symptoms were found to be less severe in C&A with EOP than in C&A at CHR-P fulfilling DSM-5–Attenuated Psychosis Syndrome criteria (p<0.001). However, the power of our analysis was lower for C&A at CHR-P than for EOP, with just six independent studies fulfilling our CHR-P inclusion criteria.

From a diagnostic perspective, we have extensively reviewed clinico-epidemiological, neurobiological and neurocognitive risk factors that increase the likelihood of experiencing negative symptoms or their greater severity. In our meta-regression analysis, sample prevalence of schizophrenia was not associated with an increased prevalence of negative symptoms. Individual studies did find a greater severity of negative symptoms in the schizophrenia subgroup. This finding suggests that negative symptoms do not only appear in schizophrenia and should be evaluated and monitored in C&A in the early stages of psychosis regardless of their diagnosis or presentation. That said, there may be some individuals in whom the therapeutic intensity in regard to pharmacological interventions and particularly antipsychotic treatment could be minimised and psychosocial interventions could be offered instead. For instance, young people with brief psychotic disorders seem to present less severe negative symptoms, not only compared to schizophrenia (p=0.006) but also compared to psychosis- not otherwise specified (p=0.02). This finding is in line with previous suggestions of offering psychosocial interventions without antipsychotic medication to individuals with brief psychotic episodes or with a shorter duration of untreated psychosis, which is in turn associated with less severe negative symptoms. Risk factors may also have an effect on the presentation of negative symptoms. For instance, C&A with EOP and obesity seemed to present with less severe negative symptoms (p=0.003). It is thus important to advance knowledge on the implementation of precision psychiatry to be able to offer state-of-the-art interventions that are personalised and needs-based. To do that, it is vital to provide mental health professionals with adequate competence and skills training to identify and manage relevant psychopathological and functional disabilities, including those related to
negative symptoms.\textsuperscript{134} Notably, the detection of negative symptoms seems to be improving in the last decades, the prevalence of negative symptoms having increased from 44\% in 1991-2000 to 70.3\% in 2011-2022, suggesting that some of these competencies and skills have been achieved by \textit{professionals}. One of the challenges in this field, regarding the acquisition of some of these competencies, is the distinction between depressive symptoms and negative symptoms, since there is a correlation between depressive symptoms and negative symptoms and \textit{since there may be some overlap, including in individuals with non-affective psychosis}.\textsuperscript{18,87,90,91} \textbf{A systematic review identified that depressed mood, hopelessness and suicidality had greater specificity for depression in patients with schizophrenia, while alogia, affective blunting and social withdrawal were more characteristic of negative symptoms.}\textsuperscript{135} These distinctions are not always easy for clinicians to make, but as a recent network analysis in adults with schizophrenia and predominant negative symptoms showed, negative symptoms appear to be an independent symptom cluster that can be delineated from depressive symptoms in the network.\textsuperscript{136} Psychometric instruments or digital tools that clearly differentiate these symptoms are required since the presence and severity of negative symptoms may overlap or covary with the severity of other symptoms (e.g. with depressive symptoms but also with positive symptoms or anxiety symptoms) and with functional impairment. Training in the use of these instruments is therefore also important. Finally, the development of a core outcome set for observational and clinical studies in EOP and CHR-P individuals as per https://www.comet-initiative.org/ that does not rely on behaviour only could reduce heterogeneity and measurement variation and improve the accuracy of the detection of negative symptoms.

From a prognostic perspective, this review provided valuable information on diagnostic stability, course and outcomes as well as on the factors that are associated with increased negative symptoms during the longitudinal follow-up. Overall, negative symptoms were characterised by consistency and stability.\textsuperscript{58,59} Interestingly, in the CHR-P field, meta-analytical evidence showed that negative symptoms improved at 12 months follow-up (g=0.496) but not at 24 months or ≥36 months compared to baseline (p>0.05) in CHR-P individuals.\textsuperscript{137} This result suggests that negative symptoms need to be monitored during the follow-up period, even if they initially improve. Some C&A with EOP or at CHR-P present with clinical risk factors for poor outcomes (e.g. prominent negative symptoms at baseline\textsuperscript{62} or long duration of untreated psychosis)\textsuperscript{39} or neurobiological risk factors for poor outcomes (e.g. frontal cortical thinness, changes in the cerebrospinal fluid)\textsuperscript{65}. \textbf{They may require additional clinical attention since their negative symptoms may deteriorate.}

Finally, from a therapeutic perspective, \textbf{we conclude} that research on preventive treatments
for C&A with EOP or at CHR-P has limited evidence compared to adults.\textsuperscript{138} In the reviewed studies in C&A with EOP, clozapine was the only medication that showed in RCTs superiority against other antipsychotic medications.\textsuperscript{69,70} However, since meta-analytical evidence shows that clozapine is associated with significant cardiometabolic, cardiac, haematological and neurological adverse effects in C&A treated with these medications,\textsuperscript{139,140} clozapine needs to be reserved for treatment-resistant cases in which they have been researched (e.g. after two previous antipsychotics have failed). Other medications, such as aripiprazole, for which a study found a better response in C&A with EOP with negative symptoms than with positive symptoms,\textsuperscript{75} may be prescribed first. Other second-generation antipsychotics (e.g. lurasidone\textsuperscript{72} and, quetiapine\textsuperscript{73,74}) have shown some benefits, but the comparisons do not clearly benefit any of them (apart from clozapine) over the others. The study of other medication groups is recommended, particularly antidepressants, which have shown to be overall effective-although with small effect size- for negative symptoms in adults.\textsuperscript{118,119} There is also insufficient evidence to recommend any specific psychosocial intervention in C&A with EOP or at CHR-P over the others. Of note, early intervention services (typically offered to adolescents and young adults with EOP/at CHR-P) have shown a reduction in negative symptom severity after 6–24 months\textsuperscript{141} compared to treatment as usual, supporting the need for funding and use of early intervention services. To advance the knowledge in the field, future research should evaluate changes in negative symptoms as their primary outcome, recruiting and selecting C&A in whom negative symptoms are predominant.

This study has several limitations that must be taken into consideration when interpreting our results. First, the sample sizes and the number of articles were limited for some of the evaluated outcomes. Importantly, only twenty independent samples provided independently meta-analysable data on the presence of negative symptoms, while most studies only reported negative symptoms as a continuous outcome. Second, participants included in the studies were heterogeneous and not selected based on the presence of negative symptoms; the studies were also heterogeneous in their design, methodology and quality, which was low in some of the included studies. Third, the threshold used to consider that negative symptoms were present varied, and some studies did not specify how they measured or defined presence of negative symptoms. Also, currently used instruments typically rely on behaviour that may have been reported and not always observed, while subjective experiences may only insufficiently be assessed. Fourth, the mean age of participants in the included studies ranged from 10–17.9 years, which was highly variable. Differences in terms of neurodevelopment and subsequent expression of negative symptoms could exist. We have mitigated against this issue with our sensitivity analyses, but some of these analyses may have been underpowered. Finally, and relatedly, as anticipated in our protocol, the amount of evidence was limited for
some outcomes and did not allow us to carry out additional meta-analyses of longitudinal data. This study also has several strengths. Among them is the fact that this is the “first in field” and most comprehensive systematic review with meta-analytical evidence to date focusing on the prevalence of negative symptoms in C&A with EOP and at CHR-P. Our database for the systematic review was large and globally representative, including 133 individual studies. We used rigorous methods and carefully reported the study quality, while providing sensitivity analyses, heterogeneity analyses and publication bias assessments. This approach has allowed us to provide state-of-the-art evidence on the current state in the field but also the challenges and gaps that future studies should address.

In conclusion, negative symptoms are at least as common in C&A with EOP as in adult-onset psychosis. Negative symptoms also appear frequently during the prodromal period in C&A at CHR-P. Negative symptoms are associated with poor outcomes, including clinical, functional and intervention outcomes. Due to limited evidence, future interventional research is required, so that C&A can receive evidence-based treatments for negative symptoms aimed at improving outcomes in this vulnerable population.
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**Data Availability:** Studies included can be found and accessed online through Google Scholar. The full text for some of the studies may not be available without a subscription. The corresponding author may be contacted.
Fig1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart outlining the study selection process.

- **Identification**
  - Records identified from:
    - Databases (n=3220)
    - Registers (n=69)
  - Records removed before screening:
    - Duplicate records removed (n=96)
    - Records marked as ineligible or removed for other reasons (n=0)

- **Screening**
  - Records screened (n=3193)
  - Records excluded (n=2904)
  - Reports sought for retrieval (n=289)
  - Reports not retrieved (n=0)
  - Reports assessed for eligibility (n=289)
    - Reports excluded:
      - Population (n=119)
      - Outcome (n=25)
      - Other reason (n=12)

- **Included**
  - Studies included in systematic review (n=133)
  - Studies included in meta-analysis (n=20)
Fig2. Negative symptom prevalence in C&A with EOP.

<table>
<thead>
<tr>
<th>Study</th>
<th>ES (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pencer 2005</td>
<td>0.493 (0.370, 0.616)</td>
</tr>
<tr>
<td>Maki 2008</td>
<td>0.900 (0.555, 0.997)</td>
</tr>
<tr>
<td>Fleischhaker 2005</td>
<td>0.716 (0.605, 0.811)</td>
</tr>
<tr>
<td>Mensi 2021 part 2</td>
<td>0.935 (0.786, 0.992)</td>
</tr>
<tr>
<td>Geon 2002</td>
<td>0.771 (0.627, 0.880)</td>
</tr>
<tr>
<td>Zakowicz 2022</td>
<td>0.968 (0.833, 0.999)</td>
</tr>
<tr>
<td>Kim 2009</td>
<td>0.409 (0.207, 0.636)</td>
</tr>
<tr>
<td>Reddy 1996</td>
<td>0.465 (0.312, 0.623)</td>
</tr>
<tr>
<td>Rapado-Castro 2010</td>
<td>0.909 (0.834, 0.958)</td>
</tr>
<tr>
<td>Jarbin 2004</td>
<td>0.261 (0.173, 0.366)</td>
</tr>
<tr>
<td>Karakus 2022</td>
<td>0.394 (0.310, 0.483)</td>
</tr>
<tr>
<td>Kafali 2019</td>
<td>0.533 (0.343, 0.717)</td>
</tr>
<tr>
<td>Downs 2019</td>
<td>0.376 (0.338, 0.415)</td>
</tr>
<tr>
<td>McClellan 1999</td>
<td>0.412 (0.276, 0.558)</td>
</tr>
<tr>
<td>DeVylder 2013</td>
<td>0.560 (0.447, 0.668)</td>
</tr>
<tr>
<td>Overall ($I^2 = 97.500%, p = 0.000$)</td>
<td>0.608 (0.464, 0.752)</td>
</tr>
</tbody>
</table>
Fig 3. Negative symptom prevalence in C&A at CHR-P.

<table>
<thead>
<tr>
<th>Study</th>
<th>ES (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spada 2016</td>
<td>0.773 (0.546, 0.922)</td>
</tr>
<tr>
<td>Giordano 2022</td>
<td>0.986 (0.924, 1.000)</td>
</tr>
<tr>
<td>Mensi 2021</td>
<td>0.745 (0.654, 0.824)</td>
</tr>
<tr>
<td>Rodriguez-Pascual 2021</td>
<td>0.764 (0.662, 0.848)</td>
</tr>
<tr>
<td>Quijada 2010</td>
<td>0.800 (0.563, 0.943)</td>
</tr>
<tr>
<td>Schneider 2019</td>
<td>0.667 (0.472, 0.827)</td>
</tr>
<tr>
<td>Overall (I^2 = 92.163%, p = 0.000)</td>
<td>0.796 (0.663, 0.929)</td>
</tr>
</tbody>
</table>
Table 1. Subgroup analyses.

<table>
<thead>
<tr>
<th>Group, subgroup</th>
<th>K</th>
<th>N</th>
<th>Meta-analysis</th>
<th>z Score</th>
<th>P</th>
<th>Heterogeneity</th>
<th>Within subgroup heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prop</td>
<td>95 CI</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Decade</td>
<td></td>
<td></td>
<td>Prop</td>
<td>95 CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1991-2000</td>
<td>2</td>
<td>94</td>
<td>0.660</td>
<td>0.536</td>
<td>0.785</td>
<td>2.969</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>389</td>
<td>0.660</td>
<td>0.432</td>
<td>0.832</td>
<td>1.384</td>
<td>0.166</td>
</tr>
<tr>
<td>2011-2022</td>
<td>11</td>
<td>1316</td>
<td>0.703</td>
<td>0.566</td>
<td>0.811</td>
<td>2.837</td>
<td>0.005</td>
</tr>
<tr>
<td>Continent</td>
<td></td>
<td></td>
<td>Prop</td>
<td>95 CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>14</td>
<td>1482</td>
<td>0.726</td>
<td>0.592</td>
<td>0.829</td>
<td>3.165</td>
<td>0.002</td>
</tr>
<tr>
<td>Asia</td>
<td>2</td>
<td>70</td>
<td>0.609</td>
<td>0.249</td>
<td>0.880</td>
<td>0.563</td>
<td>0.573</td>
</tr>
<tr>
<td>North-America</td>
<td>3</td>
<td>204</td>
<td>0.497</td>
<td>0.416</td>
<td>0.578</td>
<td>-0.073</td>
<td>0.942</td>
</tr>
<tr>
<td>Africa</td>
<td>1</td>
<td>43</td>
<td>0.465</td>
<td>-0.323</td>
<td>0.613</td>
<td>-0.457</td>
<td>0.648</td>
</tr>
<tr>
<td>Design</td>
<td></td>
<td></td>
<td>Prop</td>
<td>95 CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age range 0-18</td>
<td>13</td>
<td>1480</td>
<td>0.662</td>
<td>0.537</td>
<td>0.768</td>
<td>2.506</td>
<td>0.012</td>
</tr>
<tr>
<td>Age range &gt;18</td>
<td>5</td>
<td>197</td>
<td>0.647</td>
<td>0.510</td>
<td>0.765</td>
<td>2.104</td>
<td>0.035</td>
</tr>
<tr>
<td>Design</td>
<td></td>
<td></td>
<td>Prop</td>
<td>95 CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>6</td>
<td>314</td>
<td>0.651</td>
<td>0.528</td>
<td>0.757</td>
<td>2.384</td>
<td>0.017</td>
</tr>
<tr>
<td>Longitudinal</td>
<td>14</td>
<td>1485</td>
<td>0.663</td>
<td>0.531</td>
<td>0.774</td>
<td>2.406</td>
<td>0.016</td>
</tr>
</tbody>
</table>
Table 2. Meta-regression analyses.

<table>
<thead>
<tr>
<th></th>
<th>No. of Studies</th>
<th>$\beta$ Coefficient</th>
<th>SE</th>
<th>95% CI</th>
<th>Z-Value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year of publication</td>
<td>20</td>
<td>0.0511</td>
<td>0.0291</td>
<td>-0.0059 - 0.1082</td>
<td>1.76</td>
<td>0.0791</td>
</tr>
<tr>
<td>% of patients with schizophrenia</td>
<td>11</td>
<td>0.0004</td>
<td>0.0109</td>
<td>-0.0210 - 0.0217</td>
<td>0.03</td>
<td>0.9737</td>
</tr>
<tr>
<td>Sample size</td>
<td>20</td>
<td>-0.0022</td>
<td>0.0016</td>
<td>-0.0053 - 0.0009</td>
<td>-1.41</td>
<td>0.1572</td>
</tr>
<tr>
<td>Mean age</td>
<td>17</td>
<td>-0.1314</td>
<td>0.2488</td>
<td>-0.6190 - 0.3562</td>
<td>-0.53</td>
<td>0.5974</td>
</tr>
<tr>
<td>% males</td>
<td>18</td>
<td>0.0187</td>
<td>0.0219</td>
<td>-0.0242 - 0.0616</td>
<td>0.85</td>
<td>0.3934</td>
</tr>
<tr>
<td>% of patients on antipsychotics</td>
<td>7</td>
<td>-0.0021</td>
<td>0.0080</td>
<td>-0.0177 - 0.0136</td>
<td>-0.26</td>
<td>0.7966</td>
</tr>
<tr>
<td>Quality of the study</td>
<td>20</td>
<td>-0.0915</td>
<td>0.1386</td>
<td>-0.3631 - 0.1801</td>
<td>-0.66</td>
<td>0.5092</td>
</tr>
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</table>
References


