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Negative Symptoms and Functioning in Youth at Risk of Psychosis: A Systematic Review and Meta-Analysis

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Abstract

Aim: Youth at clinical high risk for psychosis often demonstrate significant negative symptoms and poor functioning. However, the magnitude and direction of the relationship between the two remains unknown. Therefore, the objective of this systematic review was to summarize the relationship between negative symptoms and functioning in CHR samples.

Method: Electronic databases Embase, EBM, MEDLINE, CINAHL, and PsycINFO were searched from inception. Studies were selected if they included any study that reported a relationship between negative symptoms and functioning in youth at CHR. The correlation coefficient r was converted to Cohen's d and all random effects meta-analyses were performed using the transformed values.

Results: Forty-one studies met the inclusion criteria, including a total of 4,574 clinical high risk for psychosis individuals. Negative symptom total scores were significantly associated with poorer global functioning (d , -1.40; 95% CI= -1.82, -0.98; $I^2=79.4\%$; $P<0.001$, 9 studies, N=782), social functioning (d , -1.10; 95% CI= -1.27, -0.93; $I^2=10.40\%$; $P<0.001$, 12 studies, N=811), and role functioning (d , -0.96; 95% CI= -1.17, -0.76; $I^2=41.1\%$; $P<0.001$, 9 studies, N=881). In addition, negative symptoms were consistently associated with poor premorbid functioning. When examining negative symptom domains; avolition, anhedonia, and blunted affect were each significantly and independently associated with poorer social functioning and role functioning. In terms of prediction models, negative symptoms contributed to the prediction of lower functioning across multiple studies.

Conclusion: This meta-analysis demonstrated a consistent and strong relationship between negative symptoms and functioning in youth at clinical high risk for psychosis.

Keywords

clinical high risk; functioning; negative symptoms; psychosis; role functioning; social functioning

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Author Contributions

DD was involved in the overall concept of the paper, writing, and analysis. AB and TS were involved in literature searches, data abstraction, and quality assessment. JA was involved in the overall concept of the paper and editing.

Disclosure Statement

The authors declare no conflict of interest.

1. Introduction

Negative symptoms are a significant cause of burden to both patients with schizophrenia and health-care systems.^{1, 2} Furthermore, negative symptoms are often associated with functional deficits in patients with schizophrenia,^{3, 4} with both negative symptoms and functional deficits present long before the onset of a first episode.^{5, 6} Evidence also suggests that specific negative symptom domains, such as avolition, may play a role in predicting functional outcomes in schizophrenia.⁷ Likewise, those at clinical high risk (CHR) for psychosis have both negative symptoms and functional deficits,^{8–10} in fact, one large review demonstrated that the prevalence of negative symptoms in CHR youth is higher than that of first episode patients (FEP).¹¹ However, most CHR studies continue to focus on transition and attenuated psychotic symptoms even though negative symptoms and functional deficits are leading causes for CHR youth seeking out clinical services.¹²

CHR youth often have significant negative symptoms, with one large longitudinal study indicating that over 80% of CHR youth present with at least one negative symptom of moderate severity or above at baseline.¹⁰ In addition, CHR youth present with a wide range of negative symptom domains such as flat affect, alogia, anhedonia, avolition, and asociality.^{13, 14} CHR youth also present with deficits in global functioning,¹⁵ deficits in social functioning¹⁶ (i.e., level of social contact, friendships) and deficits in role functioning (i.e., level of functioning at school or work) when compared to their non-psychiatric peers.¹⁶ Moreover, negative symptoms have been shown to predict poor functioning in CHR more so than positive symptoms and despite established relationships between cognition and functioning in CHR, negative symptoms both mediate and are primary in this relationship^{17–20} Both negative symptoms and functioning have been shown to reduce quality of life and impact long-term outcomes in CHR individuals,^{21–24} thus a greater understanding of the association between negative symptoms and functioning in CHR youth may help with the development of more precise treatment targets.

However, no meta-analysis has been conducted looking specifically at the relationship between negative symptoms and functioning in CHR youth. Thus, the aim of this current review was to: (1) provide a systematic review of studies examining the relationship between negative symptoms and functional deficits; (2) conduct an aggregated meta-analysis to further define the relationship between negative symptoms and functioning in CHR samples; and (3) conduct an aggregated meta-analysis to examine whether any negative symptom domains (i.e., anhedonia) were associated with functional deficits in CHR.

2. Method

2.1 Protocol

This review protocol was prospectively registered with the PROSPERO database of systematic reviews. This systematic review and meta-analysis was conducted in accordance with the meta-analysis of observational studies in epidemiology (MOOSE) guidelines²⁵ and preferred reporting for systematic reviews and meta-analyses (PRISMA).^{26, 27}

2.2 Search Strategy

A comprehensive search of the literature was conducted in the following online databases: PsycINFO, MEDLINE, Embase, EBM and CINAHL from inception to June 2019 with no geographical or language restrictions. An electronic database search example is provided in the Supplementary Material. After duplicates were removed, two reviewers (A.B. and D.D.) independently performed title and abstract screening using the online Covidence systematic review software.²⁸ Full text articles were then independently reviewed by the same two reviewers to determine inclusion in this systematic review and selected in accordance to the selection criteria outlined below. Finally, the reference lists of included articles were hand searched for relevant studies not found through online database searching.

2.3 Selection Criteria

Studies that met the following criteria were considered eligible for inclusion in this systematic review by two reviewers (A.B. and D.D.): (1) research including participants at risk for psychosis meeting criteria for either CHR, ultra-high-risk (UHR), attenuated psychosis syndrome (APS), or at-risk mental state (ARMS); (2) reported negative symptoms; (3) reported the association between negative symptoms and functioning, (4) reported a mean age between 12–30 years, and (6) study design was either cross-sectional or longitudinal in nature. In addition, the following exclusion criteria was applied to all studies: (1) intervention studies due to their potential impact on either negative symptoms or functioning; (2) ineligible study design (case reports, review articles, opinion pieces, conference abstracts, imaging studies, and editorials without original data), and (3) insufficient data for the meta-analysis. Initial agreement on title/abstract screening was assessed using the kappa statistic for interrater reliability between reviewers. Disagreements were first discussed in a group meeting and the final decision for inclusion was made by D.D.

2.4 Data Extraction

Data abstraction was completed in duplication (A.B. and T.S.) including the following study characteristics: first author, year of publication, country, study design, sample size, CHR sample size, age (mean $\pm$ SD), number of males/percent male, negative symptom scores (mean $\pm$ SD), negative symptom scale, and key findings associated with negative symptoms. For the meta-analysis, the following data was extracted: (1) first author, (2) year of publication, (3) correlation coefficient (r), (4) CHR sample size, (5) standard error, (6) Fisher's Z scores, (7) t-values (t), p-values (p), (8) direction of effect, (9) negative symptom scale, (10) negative symptom variable (e.g., total score), (11) functioning scale, and (12) prediction analysis (yes/no).

2.5 Risk-of-Bias Assessment

Included studies were independently evaluated for quality by two reviewers (A.B. and D.D.). Both cross-sectional and longitudinal studies were assessed for quality using a modified Downs and Black instrument.²⁹ The modified Downs and Black checklist utilizes 14-items to evaluate cross-sectional studies and 16-items for longitudinal studies, providing a total score out of 15 or 17 points for each study with higher scores indicating greater quality.

The Downs and Black instrument was utilized due to its ability to assess studies across the five domains of study quality, external validity, study bias, confounding and selection bias, and the power of the study. This checklist contains yes (1) or no (0) questions which are applied to a series of thorough questions regarding the quality of each study (i.e., Is the hypothesis/aim/objective of the study clearly described?). Studies were not excluded from this systematic review and meta-analysis based on the quality assessments.

2.6 Data Synthesis and Analysis

Due to heterogeneity between studies, DerSimonian and Laird³⁰ random-effects meta-analyses were performed on eligible studies to estimate pooled effect sizes and 95% CIs for each study and then presented by subgroup based on their respective association (e.g., Negative Symptom Total Scores and Global Functioning). The Cohen *d* method was used to calculate the effect sizes for all meta-analyses in this review.³¹ Cohen *d* was selected due to the heterogeneous nature of both the negative symptom scales and functioning scales reported in the current studies and all studies having sample sizes ($n \geq 20$). The majority of studies in this meta-analysis reported the Pearson correlation coefficient (*r*), which was transformed into Cohen *d* using the following formula $d = 2r / [1 - r^2]$ and the variance was calculated by $V_d = 4V_r / (1 - r^2)^3$ where V_r represents the variance of r_p . As an approximation the same conversion was applied to Spearman correlation coefficients since it is equivalent to the Pearson correlation coefficient (*r*) when using rank data or is marginally smaller if the data have a binomial distribution.³² Next, in one study the reported R^2 was converted to *r* from a stepwise regression model³³ and the *t*-value in an ANOVA from another study was transformed into *r*,³⁴ both the R^2 and *t*-value were subsequently converted to Cohen *d*.

Two or more independent studies with similar observations (i.e., two studies examining Negative Symptom Total Scores and Role Functioning) were required to be included in the aggregated meta-analyses. If applicable, scales were inverted to match the direction of effect of the majority of scales. To avoid double-counting, in the case of two or more studies reporting similar observations in the same sample the data from the largest sample was utilized. The majority of studies included were cross-sectional in nature and thus baseline associations were preferentially selected in the case where multiple timepoints were reported to ensure continuity. Where applicable, we examined the relationship between functioning and negative symptom domains based on the NIMH-MATRICES five negative symptom domains, which include asociality, anhedonia, avolition, blunted affect, and alogia².

For publication bias, funnel plots were stratified by associations, at least 10 studies were required to visually assess funnel plots for asymmetry³⁵ and publication bias in these cases was further explored using Egger's test for asymmetry.³⁶ Statistical heterogeneity was examined using the I^2 statistic, with I^2 50% deemed moderate, and I^2 75% high heterogeneity. All analyses were performed in STATA (v.13).³⁷

3. Results

3.1.1 Search Yield

Through electronic database searching 2,279 records were identified and after duplicate references were removed a total of 1,426 abstracts and titles were screened. The level of agreement between the two reviewers for screening was high ($\kappa=0.88$). A total of 47 studies were retrieved and reviewed in full text. Altogether, 41 studies met the inclusion criteria, including a total of 4,574 CHR individuals, of which 21 studies were included in the meta-analysis, see Figure 1.

3.1.2 Meta-Analysis Study and Participant Characteristics

Studies included in the meta-analysis portion of this review are described in Table 1, most studies were conducted in North America ($n=9$),^{38–46} followed by Asia ($n=5$),^{47–51} Europe ($n=4$),^{33, 34, 52, 53} and Australia ($n=3$).^{54–56} There were fourteen cross-sectional studies and seven longitudinal studies. Further, there was a total of 1,668 CHR patients included in the meta-analyses, ranging from sample sizes of 27–241 participants in individual studies. The mean age was 19.53 years and percentage of males was 57%.

3.1.4 Risk-of-Bias

Studies included in the meta-analyses were assessed with the Downs and Black instrument (Table 2a and Table 2b). For cross-sectional studies, the average Downs and Black score was 14.64/15, indicating relatively good quality across studies. Although most cross-sectional studies were of good quality one failed to report potential confounders, two failed to adjust for potential confounders, and one did not report actual probabilities. For longitudinal studies, the average Downs and Black score was 15/17, indicating relatively good quality across studies as well. However, five of the seven longitudinal studies did not report lost to follow-up nor were losses to follow-up taken into account in the analysis and two of the studies did not adjust for confounders.

3.1.5 Publication Bias

For publication bias, visual inspection of the funnel plot for the outcome of negative symptoms and social functioning ($k=12$) did not indicate asymmetry (see Figure 2), which was further corroborated by a non-significant Egger's test ($p=0.266$). Due to the limited amount of studies asymmetry was not assessed for the remainder of associations ($k<10$).

3.1.6 Negative Symptom Total Scores and Functioning

Negative symptom total scores were significantly associated with poorer global functioning ($d, -1.40$; 95% CI= $-1.82, -0.98$; $r, -0.57$; $\hat{P}=79.4\%$; $P<0.001$, 9 studies, $N=782$; Figure 3a), social functioning ($d, -1.10$; 95% CI= $-1.27, -0.93$; $r, -0.48$; $\hat{P}=10.4\%$; $P<0.001$, 12 studies, $N=811$; Figure 3b), and role functioning ($d, -0.96$; 95% CI= $-1.17, -0.76$; $r, -0.43$; $\hat{P}=41.1\%$; $P<0.001$, 9 studies, $N=881$; Figure 3c). Due to lack of data one study was excluded from the analysis but reported a non-significant relationship between negative symptom total scores and social functioning.⁵⁷

3.1.7 Avolition and Functioning

Avolition was significantly associated with poorer social functioning (d , -0.80 ; 95% CI = $-1.45, -0.15$; r , -0.37 ; $I^2=73.4\%$; $P<0.05$, 2 studies, $N=228$) and role functioning (d , -0.82 ; 95% CI = $-1.10, -0.53$; r , -0.38 ; $I^2=0.0\%$; $P<0.001$, 2 studies, $N=228$), see figures 4a-b. Although not included in the aggregated meta-analyses, one study reported a significant relationship between avolition and global functioning (d , -1.71 ; 95% CI = $-2.2, -1.21$; r , -0.65 ; $P<0.001$, 1 study, $N=110$).⁵⁸

3.1.8 Anhedonia and Functioning

Anhedonia was significantly associated with poorer social functioning (d , -0.98 ; 95% CI = $-1.66, -0.29$; r , -0.44 ; $I^2=85.5\%$; $P<0.05$, 5 studies, $N=366$) and role functioning (d , -0.82 ; 95% CI = $-1.09, -0.56$; r , -0.38 ; $I^2=0\%$; $P<0.001$, 3 studies, $N=264$), see figures 4c-d.

3.1.9 Blunted affect and Functioning

Blunted affect was significantly associated with poorer social functioning (d , -0.89 ; 95% CI = $-1.18, -0.60$; r , -0.41 ; $I^2=0\%$; $P<0.001$, 2 studies, $N=228$) and role functioning (d , -0.66 ; 95% CI = $-0.94, -0.38$; r , -0.31 ; $I^2=1.0\%$; $P<0.001$, 2 studies, $N=228$), see figures 4e-f.

3.2.1 Qualitative Synthesis

Qualitative synthesis of studies not included in the meta-analysis portion of this review are described in supplementary table 1, ($n=21$). These studies were not included in the meta-analysis primarily due to study design leading to insufficient data. Important highlights of the relationship between negative symptoms and functioning in these studies are outlined below in sections 3.2.2 to 3.2.4.

3.2.2 Negative Symptoms and Premorbid Functioning

Two studies demonstrated that premorbid social maladjustment was associated with social anhedonia and reduced expression of emotion^{59, 60} and in another study poor premorbid social adjustment predicted less improvement in negative symptoms.⁶¹ The fourth study showed that poorer premorbid functioning was significantly correlated with both increased negative symptom severity and poorer functioning.⁶²

3.2.3 Negative Symptoms and Functioning in CHR Subgroups

A variety of studies examined negative symptoms and functioning by describing subgroups. First, in one study CHR individuals who showed functional improvement had a larger decline in negative symptoms compared to those who did not improve.⁶³ Second, another study demonstrated that a poor outcome group had higher negative symptoms and lower functioning compared to a good outcome group.⁶⁴ A third study showed that patients with poor social outcomes had more severe negative symptoms, disorganized symptoms, and poorer social functioning at baseline compared to those with good social outcomes.⁸ Next, one study demonstrated that a group with primarily negative symptoms had an increased risk of functional disability relative to a positive symptom group,⁶⁵ which was further corroborated by a study of CHR individuals with persistent negative symptoms who had

markedly poorer functioning compared to those without persistent negative symptoms.⁶⁶ Lastly, a study that examined the difference between those who transitioned to psychosis within the first 6 months (i.e., short-term converters) versus those who transitioned to psychosis between 7–30 months (i.e., long-term converters) demonstrated that long-term converters had more severe negative symptoms and poorer role functioning comparatively.⁶⁷

3.2.3 Mediation, Factor, and Latent Class Analyses

Other notable points are that in mediation analyses one study demonstrated that negative symptoms mediated the relationship between neurocognition and functioning⁶⁸ while in another study the relationship between the personality trait interpersonal sensitivity and social functioning was not mediated by negative symptoms.⁶⁹ Next, a factor analysis indicated a two factor model consisting of two negative symptom dimensions of volition and emotion.¹⁴ The emotional factor in this model was associated with poor social functioning and the volition factor was associated with poor role functioning. Lastly, a latent class analysis indicated that individuals in class 3 (negative-neurocognitive) had significant social and academic maladjustment scores when compared to class 1 (mild symptoms) and class 2 (paranoid-affective).⁷⁰

3.2.4 Prediction Models

Several studies demonstrated that negative symptoms contributed to the prediction of lower functioning. One study demonstrated that avolition, attention, and motor-coordination were significant predictors of poorer functioning⁷¹ while another study showed that anhedonia-asociality, attention disturbances, and disorder of thought content predicted poorer functioning.⁷² Next, a combination of increased negative symptoms and reduced performance on a verbal recall task was the best predictor of poor functional outcome.⁶⁴ Other studies have shown that having longer negative symptom duration predicted poor social functioning⁷³ and that negative symptom severity uniquely predicted poor social functioning.⁷⁴

4. Discussion

This meta-analysis examined the relationship between negative symptoms and functioning in youth at CHR for psychosis. The results indicate that, in CHR samples, severity of negative symptoms was significantly associated with deficits in global functioning, this association demonstrated the largest effect size. Next, in order of largest effect sizes, negative symptoms were significantly associated with deficits in social functioning, followed by deficits in role functioning. When examining the relationship between negative symptom domains and functioning, the largest effect size was found between anhedonia and social functioning followed by blunted affect and social functioning, avolition and role functioning, anhedonia and role functioning, avolition and social functioning, and lastly blunted affect and role functioning. When examining studies included in the qualitative synthesis, we found a clear relationship between premorbid functioning and negative symptoms, increased negative symptoms in CHR subgroups with poorer functioning, and that negative symptoms contributed to the prediction of poorer functioning in CHR samples.

Consistent with schizophrenia research, negative symptoms were significantly associated with deficits in global, social, and role functioning in CHR samples.^{3, 4, 19, 75–79} One meta-analysis of 23 schizophrenia studies ($n = 2,341$) found a significant relationship between negative symptoms and functioning ($r = -0.42$), which converts to a Cohen's d of -0.93 . Comparatively, this means that negative symptoms and functioning appear to have a much stronger relationship in CHR individuals ($d, -1.40$) when compared to patients with schizophrenia. This may be of concern in that the current focus of identification of CHR youth is on attenuated psychotic symptoms and the focus of treatment studies to date has primarily been transition to a psychotic disorder. Adding to this, the majority of CHR youth will not develop a psychotic disorder but will continue to have both functional deficits and negative symptoms.⁸⁰

In patients with psychosis, factor analyses of negative symptom domains suggest that two distinct negative symptom dimensions exist: experiential negative symptoms consisting of anhedonia, avolition, and asociality and expressive negative symptoms consisting of blunted affect and alogia.^{81–84} In the current meta-analysis, we examined three of the five negative symptom domains including anhedonia, avolition, blunted affect, and their relationship with either social or role functioning. Anhedonia, avolition, blunted affect were all significantly associated with both social and role functioning in the meta-analyses. These results echo studies in first episode psychosis and schizophrenia patients that have shown a relationship between avolition and functional outcomes,^{7, 85–87} anhedonia and functional outcomes,^{88–90} and blunted affect and functional outcomes.⁹¹ In the current meta-analysis no studies examined the relationship between the domains of alogia nor asociality and functioning explicitly. However, one study included in the qualitative synthesis examined a two-factor negative symptom structure of experiential versus expressive negative symptoms and their relationship with functioning in CHR participants.⁷⁴ The authors of this study concluded that experiential negative symptoms appear to be more important in determining social functioning relative to expressive negative symptoms, which may help with the development of more precise treatment targets. However, studies examining experiential versus expressive negative symptoms in CHR are rare and thus more studies are required to further understand their relationship to functional deficits.

Other notable points are that poor premorbid functioning was consistently associated with negative symptoms in CHR samples, findings which are similar to those found in schizophrenia studies.^{92, 93} Similarly, in CHR subgroups a clear pattern emerged in that participants grouped together based on poor functional outcomes consistently had worse negative symptoms and vice versa. These results are similar to both persistent negative symptom and deficits syndrome subgroup studies in schizophrenia in that they often demonstrate greater deficits in functioning.^{71–76} In terms of prediction models, negative symptoms contributed to the prediction of lower functioning across multiple studies. These findings are similar to research conducted in patients with schizophrenia where negative symptoms have consistently been shown to be a significant contributor to lower functioning^{94–96} and in some cases negative symptoms demonstrate a stronger risk factor for lower functioning than positive psychotic symptoms in schizophrenia.⁹⁵ In a similar vein, one of the CHR studies demonstrated that attenuated psychotic symptom severity predicted social or role functioning whereas negative symptom duration predicted poor social functioning.⁷³

In this review negative symptoms tended to have larger effect sizes in relation to deficits in social functioning then role functioning, with the largest effect between anhedonia and social functioning. Thus, it may be the case that targeting anhedonia in treatment trials may help with improving social deficits in youth at CHR for psychosis.

Some important implications from this review may help shape our knowledge of negative symptoms in CHR. As stated functioning appears to be more related to negative symptoms in CHR when compared to those with schizophrenia however there no effective treatment for negative symptoms nor functioning in CHR. The majority of clinical trials to date have not focused on treatments that will alleviate negative symptoms in CHR nor selected for individuals with negative symptoms, and the primary focus in the detection phase and for meeting CHR criteria is to capture those with positive symptoms not negative symptoms. Thus, it is possible that due to the emphasis on attenuated psychotic symptoms that some young people with more severe negative symptoms and less attenuated psychotic symptoms are missed. However, the reality is that many CHR youth will present with negative symptoms upon initial presentation and some will even develop persistent negative symptoms. Those who do develop persistent negative symptoms have significantly worse functional outcomes but do not appear to have a higher risk of transition to psychosis compared to those without persistent negative symptoms.

4.1 Strength and Limitations

This systematic review and meta-analysis included 41 studies that examined negative symptoms and their association with different types of functioning with more than 4,500 participants at CHR for psychosis. The electronic search to identify studies included several databases, studies were reviewed in duplicate, and this review followed both MOOSE and PRISMA guidelines. To our knowledge this the first systematic review and meta-analysis that explicitly examines the association between negative symptoms and functioning in youth at CHR for psychosis. However, this review has several important limitations to consider.

First, the summary of a systematic review and meta-analysis is only as good as the quality of individual studies included in a review, which in this case the majority of studies were cross-sectional in nature. Cross-sectional studies are difficult to interpret in that it is often challenging to know whether the exposure or outcome came first. However, in the current meta-analysis we evaluated the cross-sectional studies with the Downs and Black instrument which assesses the methodological quality of the included studies and the average score was quite high indicating good quality. Next, in the seven longitudinal studies included in this meta-analysis most did not report how many patients were lost to follow-up. This may be of concern as it can impact a study's validity because participants lost to follow-up may have a different prognosis than those who complete the study. Despite this limitation, the Downs and Black instrument indicated an overall good methodological quality for the longitudinal studies included in this review as well.

Second, we pooled several negative symptoms scales, which may be important to consider when interpreting the results from the present meta-analysis. The Scale of Psychosis-risk Symptoms (SOPS) ⁹⁷ negative symptom scale was the most commonly used measure

for negative symptoms in this review. According to researchers,⁹⁸ the negative symptoms measured by the SOPS may not be directly measuring the NIMH-MATRICES five negative symptom domains, which include asociality, anhedonia, avolition, blunted affect, and alogia.² As a consequence, it has been suggested that the SOPS item N3 [Expression of Emotion] combines blunted affect, poverty of speech, and asociality into one item.⁹⁸ Next, the SOPS item N6 [Occupational Functioning] is a measure of role functioning and not a negative symptom measure, this may have inflated the association between negative symptom total scores and functioning in the current meta-analysis. However, despite this limitation of the SOPS in measuring negative symptoms it has been shown to have good convergent validity with both the Prodromal Inventory of Negative Symptoms (PINS) and the adapted version of the Brief Negative Symptom Scale (BNSS).⁹⁹ Next, the Scale for the Assessment of Negative Symptoms (SANS)¹⁰⁰ was the second most commonly used scale. Although the SANS is commonly used in CHR studies it was designed specifically for use in schizophrenia and first episode psychosis patients.¹⁴ Another issue that arises from using the SANS to measure negative symptoms is that it does not align with the NIMH-MATRICES five negative symptom domains consensus in that it includes an additional negative symptom item attention. Lastly, the Comprehensive Assessment of At-Risk Mental States (CAARMS)¹⁰¹ was developed for use in CHR samples and measures negative symptom domains of alogia, avolition/apathy, and anhedonia. The CAARMS also measures observed blunted affect however this is categorized on the emotional disturbance subscale and not on the negative symptom subscale. One critique of the CAARMS negative symptom subscale is that it has been shown to have high correlations with both positive symptoms and depression,¹⁰² and does not include asociality and blunted affect, thus it may not be adequately capturing negative symptoms. Therefore, researchers may want to consider if the negative symptom scale they wish to employ measures the five negative symptom domains in order to obtain an accurate representation of the negative symptom domains in CHR studies.

Third, this review coalesced several functioning scales, which may have important implications when considering the results. For global functioning, the Global Assessment of Functioning Scale (GAF) and Social and Occupational Functioning Assessment Scale (SOFAS)¹⁰³ were the most commonly used scales. Notably, the GAF is heavily influenced by the severity of psychiatric symptoms whereas the ratings on the SOFAS are not directly influenced by the severity of symptoms. Next, for social functioning, the Global Functioning: Social (GF:S)³⁹ was the most commonly used scale followed by the Social Adjustment Scale (SAS),¹⁰⁴ WHOQOL-BREF social relationships,¹⁰⁵ Social Functioning Scale (SFS),¹⁰⁶ and the Social Network Index (SNI).¹⁰⁷ While all the scales are geared towards measuring social functioning or some component of social functioning only the GF:S was designed for measuring social functioning in CHR samples whereas the rest were developed for either schizophrenia samples, general psychiatric patients, and individuals with substance abuse disorders. Therefore, many of these scales have been tested in other samples (i.e., schizophrenia) who are often older than CHR participants and thus have elements in their designs that may not be suitable for CHR participants. Researchers should consider if the social scale they choose to use is sensitive, comprehensive, and applicable (e.g., social media interactions) in order to detect social functioning in CHR youth. Lastly,

for role functioning the Global Functioning: Role (GF:R)³⁹ was the most commonly used scale followed by SFS: employment / occupation item, the instrumental role functioning subscale by Heinrichs et al. 1984, and the CAARMS impaired role functioning. In a similar vein, the role functioning scales are problematic in that only the GF:R and CAARMS impaired role functioning were designed to measure role functioning in CHR samples while the others were designed for patients with schizophrenia.

Fourth, three of the meta-analyses demonstrated a significant amount of high heterogeneity as measured by the I^2 , for the associations between avolition and social functioning, anhedonia and social functioning, and negative symptom total and global functioning. For the associations between avolition and social functioning and anhedonia and social functioning the meta-analyses had very few studies, as such the I^2 may not be an accurate measure of heterogeneity,¹⁰⁸ however even in small meta-analyses such as these two it has been suggested that it is better to have some estimate of I^2 than to have no estimate at all.¹⁰⁸ For anhedonia and social functioning, we performed a post-hoc sensitivity analysis and found that by dropping one study,¹⁰⁹ the heterogeneity dropped considerably ($I^2 = 26.1\%$) while the association remained significant ($d, -1.35$; 95% CI= $-1.68, -1.02$; $P < 0.01$).

Fifth, unfortunately due to study design which led to insufficient data many studies were only included in the qualitative synthesis. However, these studies provided invaluable insights into the relationship between negative symptoms and functioning as outlined in the qualitative synthesis portion of this review.

Sixth, due to the limited amount of studies included in the meta-analysis meta-regression was not performed to examine the potential impact of specific instruments (i.e., social functioning scales, negative symptom scales), year of publication, and the quality of included studies.

4.2 Directions for Future Research

The results of this systematic review and meta-analysis may lead to some possibilities for future research. First, future studies may wish to investigate and employ more specific assessments of negative symptoms (i.e., alogia and asociality) to further elucidate which negative symptoms might be more related to functioning in CHR participants and further expand this research into how functioning relates to experiential versus expressive negative symptoms as studies are currently limited. Second, given the strong relationship between negative symptoms and functioning with no effective treatments to date for either,^{110–112} future clinical trials may want to design interventions that are primarily geared towards impacting both negative symptoms and functioning.

4.3 Conclusions

This meta-analysis demonstrates a consistent and strong relationship between total negative symptoms and poor global, social, and role functioning. Moreover, anhedonia, avolition, and blunted affect were all significantly and independently associated with poor social and role functioning.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Flow Diagram

Figure 2.
Funnel Plot Stratified by Association

Figure 3.
Negative Symptom Total and Functioning Forest Plots

Figure 4.
Negative Symptom Domains and Functioning Forest Plots

Table 1.

Studies examining negative symptoms and functioning in CHR included in meta-analysis (k=21).

Reference + Year	Country	Study Design	Sample Size	CHR Participants			Negative Symptom Measure (s) Examined in Meta-analysis	Functioning Measure (s) Examined in Meta-analysis
				N	Age (M,SD)	Male (N, %)		
1. Corcoran et al. (2011)	USA	Cross-sectional	78	56	19.6 (3.6)	43(77)	SOPS: negative symptoms	SAS-SR
2. Comblatt et al., (2007)	USA	Longitudinal	165	121	16.65 (NR)	79(65)	SOPS: negative symptoms	GAF, GF:S, GF:R
3. Cotter et al., (2017)	Australia	Cross-sectional	30	30	19.1(2.8)	14(47)	SANS	GF:S
4. Cressman et al., (2015)	USA	Cross-sectional	99	62	20.9 (0.4)	47 (76)	Chapman Revised Social Anhedonia Scale	SAS-SR
5. Dominguez-Martinez et al., (2015)	Spain	Cross-sectional	40	40	21(4.1)	27(67.5)	CAARMS: negative symptoms	WHOQOL-BREF social relationships
6. Fulford et al., (2013)	USA	Cross-sectional	186	98	17.7(4.2)	58(59.2)	SOPS: negative symptoms	GAF, GF:S, GF:R
7. Gur et al. (2015)	USA	Cross-sectional	92	29	18.9(2.9)	15(52)	SOPS: negative symptoms	GAF
8. Kim et al. (2013)	South Korea	Cross-sectional	107	60	19.7(3.3)	35(58)	SOPS: negative symptoms	Interpersonal Relationships and Instrumental Role functioning subscales by Heinrichs et al. 1984
9. Lee et al., (2017)	South Korea	Cross-sectional	128	63	19.7(3.5)	38(60.3)	SANS; SANS: Avolition-apathy; SANS Affective Flattening	GF:S, GF:R
10. Lin et al., (2013)	Australia	Longitudinal	228	228	25.7(4.9)	93(40.8)	SANS	SOFAS
11. Meyer et al. (2014)	USA + Canada	Longitudinal	167	167	18.2(4.9)	107(64)	SOPS: negative symptoms; SOPS social anhedonia; SOPS Avolition; SOPS Expression of Emotion	GF:S, GF:R
12. Niendam et al., (2006)	USA	Cross-sectional	45	45	17.7(4)	29(64)	SOPS: negative symptoms	SCOS and SAS
13. Pelizza et al., (2019)	Italy	Longitudinal	123	44	15.4(1.6)	18(40.9)	CAARMS item 4.3 "Anhedonia"	CAARMS impaired role functioning, and WHOQOL-BREF social relationships
14. Robustelli et al., (2018)	USA	Cross-sectional	85	44	19.2(1.7)	26(59)	SOPS: negative symptom item social anhedonia	Social Network Index variable number of close friends
15. Seo et al., (2018)	South Korea	Cross-sectional	100	57	20.5(3.5)	35(61.4)	SANS; Anhedonia- Asociality	GF:S, GF:R
16. Shim et al. (2008)	South Korea	Cross-sectional	94	32	21(3.9)	19(59)	CAARMS: negative symptoms	SFS and SFS; Employment / Occupation
17. Shin et al. (2016)	South Korea	Longitudinal	75	47	19.3(3.3)	33(70)	SOPS: negative symptoms	GAF, SFS, SFS; Employment / Occupation
18. Willhite et al., (2008)	USA	Longitudinal	68	68	17.0(NR)	49(72)	SOPS: negative symptoms	GAF

Reference + Year	Country	Study Design	Sample Size	CHR Participants			Negative Symptom Measure (s) Examined in Meta-analysis	Functioning Measure (s) Examined in Meta-analysis
				N	Age (M,SD)	Male (N, %)		
19. Cotter et al., 2016	Australia	Longitudinal	268	246	18.72(NR)	115(46.7)	SANS	Role functioning measured by the Occupational Subscale by Heinrichs et al. 1984
20. Svirskis et al., 2007	Finland	Cross-sectional	133	133	NR	43(32.3)	SOPS: negative symptoms	GAF
21. Glenthøj et al., 2016	Denmark	Cross-sectional	95	65	24.6(4.2)	29(44.6)	SANS	SOFAS, GF:S, GF:R

Abbreviations: CHR= clinical high risk; CAARMS= Comprehensive Assessment of At-Risk Mental States; GAF= Global Assessment of Functioning; GF:R=Global Functioning; Role GF:S=Global Functioning; Social; SAS-SR=Social Adjustment Scale–Self-Report; SANS= The Scale for the Assessment of Negative Symptoms; SCOS=The Strauss and Carpenter Prognostic Scale; SFS= Social Functioning Scale; SOPS= Scale of Psychosis-risk Symptoms; SOFAS= The Social and Occupational Functioning Assessment Scale; WHOQOL-BREF= The World Health Organization Quality of Life

Table 2a.

Quality assessment checklist for cross-sectional studies included in meta-analysis (k=14).

Study	1.Aims	2.Measures	3.Characteristics	5.Confounders	6.Findings	7.Random variability	10.Probabilities	11.Representative sample	12.Representative accepted
1. Corcoran et al. (2011)	1	1	1	2	1	1	1	1	1
2. Cotter et al., (2017)	1	1	1	0	1	1	1	1	1
3. Cressman et al., (2015)	1	1	1	2	1	1	1	1	1
4. Dominguez-Martinez et al., (2015)	1	1	1	2	1	1	1	1	1
5. Fulford et al., (2013)	1	1	1	2	1	1	1	1	1
6. Gur et al. (2015)	1	1	1	2	1	1	1	1	1
7. Kim et al. (2013)	1	1	1	2	1	1	1	1	1
8. Lee et al., (2017)	1	1	1	2	1	1	1	1	1
9. Niendam et al., (2006)	1	1	1	2	1	1	1	1	1
10. Robustelli et al., (2018)	1	1	1	2	1	1	0	1	1
11. Seo et al., (2018)	1	1	1	2	1	1	1	1	1
12. Shim et al. (2008)	1	1	1	2	1	1	1	1	1
13. Svirskis et al., (2007)	1	1	1	2	1	1	1	1	1
14. Glenthøj et al., 2016	1	1	1	2	1	1	1	1	1
TOTAL	14	14	14	26	14	14	13	14	14

Notes: “1” = Yes; “0” = No; “2” = Q5 Confounders listed and described in this sample; “-” = Unable to determine and counts as 0. Questions 4, 8, 14, 15, 17, 19, 21, 22, 23, 24, and 27 were not used because the studies included in the meta-analysis were not interventional and Questions 9 & 26 were not used due to the cross-sectional nature of these studies. Questions 1, 2, 3, 5, 6, 7, 10, 11, 12, 13, 16, 18, 20, and 25 add to a maximum total possible score of 15.

Table 2b.

Quality assessment checklist for longitudinal studies included in meta-analysis (k=7).

Study	1.Aims	2.Measures	3.Characteristics	5.Confounders	6.Findings	7.Random variability	9.Lost to follow-up	10.Probabilities	11.Representative sample	12.Representative accepted
1. Cornblatt et al., (2007)	1	1	1	2	1	1	0	1	1	1
2. Lin et al., (2013)	1	1	1	1	1	1	0	1	1	1
3. Meyer et al. (2014)	1	1	1	2	1	1	1	1	1	1
4. Pelizza et al., (2019)	1	1	1	2	1	1	0	1	1	1
5. Shin et al. (2016)	1	1	1	2	1	1	0	1	1	1
6. Willhite et al., (2009)	1	1	1	2	1	1	1	1	1	1
7. Cotter et al., (2016)	1	1	1	2	1	1	0	1	1	1
TOTAL	7	7	7	13	7	7	2	7	7	7

Notes: "1" = Yes; "0" = No; "2" = Q5 Confounders listed and described in this sample; "-" = Unable to determine and counts as 0. Questions 4, 8, 14, 15, 17, 19, 21, 22, 23, 24, and 27 were not used because the studies included in the meta-analysis were not interventional. Questions 1, 2, 3, 5, 6, 7, 9, 10, 11, 12, 13, 16, 18, 20, 25, 26 add to a maximum total possible score of 17.