2020-07-02

Negative Symptoms in Youth at Risk of Psychosis

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Negative Symptoms in Youth at Risk of Psychosis

by

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A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE

DEGREE OF DOCTOR OF PHILOSOPHY

GRADUATE PROGRAM IN MEDICAL SCIENCE

CALGARY, ALBERTA

JULY, 2020

Abstract

Youth at clinical high risk (CHR) for psychosis often demonstrate significant negative symptoms but the impact of treatment on negative symptoms remains unknown. Investigations into possible mechanisms that may contribute to the development, maintenance, and exacerbation of negative symptoms in CHR youth are needed as well. One such area that remains understudied is persistent negative symptoms (PNS) in those at CHR . In addition, functioning, neurocognition, defeatist beliefs, self-efficacy, and early maladaptive schemas have been shown to contribute to negative symptoms in schizophrenia but these associations with negative symptoms remain understudied in CHR for psychosis youth.

In this manuscript based thesis we conducted a systematic review and network meta-analysis of all intervention studies examining negative symptom outcomes in youth at CHR for psychosis. Next, in a large longitudinal cohort generalized linear mixed models for repeated measures were used to examine changes over time between a PNS group vs a non-PNS group on functioning, neurocognition, and defeatist beliefs. In the third study, we conducted a systematic review and meta-analysis to summarize the relationship between negative symptoms and functioning in CHR samples. In the final study, the aim was to examine if negative symptoms were associated with defeatist beliefs, self-efficacy, and early maladaptive schemas in CHR youth.

In the network meta-analysis no treatments were found to significantly reduce negative symptoms and the majority of treatment trials were not designed to target negative symptoms. In the longitudinal cohort, PNS resulted in significant and persistent functional impairment, which remained when controlling for persistent depressive

symptoms. For the systematic review and meta-analysis, negative symptom total scores were significantly associated with poorer global functioning, social functioning, and role functioning. In the final study, asocial beliefs, social self-efficacy and maladaptive schemas about the self were significantly related to total negative symptom scores.

With no treatments established to help negative symptoms and given their significant relationship with functional impairments, an unfortunate trajectory emerges for CHR youth with negative symptoms in that they require treatments that may alleviate their symptoms and improve their day to day lives. Thus, psychosocial interventions may wish to target asocial beliefs, social self-efficacy, and maladaptive schemas in effort to reduce negative symptoms in those at CHR for psychosis.

Preface

Chapter Two of this thesis has been published as; Daniel Devoe; Aaron Peterson; Jean Addington (2017). Negative Symptom Interventions in Youth at Risk of Psychosis: A Systematic Review and Network Meta-Analysis. Schizophrenia Bulletin.

Chapter Three Research has been published as; Daniel Devoe; Lu Lui; T.D. Cannon; K.S. Cadenhead; B.A. Cornblatt; T.H. McGlashan; D.O. Perkins; L.J. Seidman; M.T. Tsuang; S.W. Woods; E.F. Walker; D.H. Mathalon; C.E. Bearden; Jean Addington (2020). *Persistent Negative Symptoms in Youth at Clinical High Risk for Psychosis: A Longitudinal Study.* Schizophrenia Research.

Chapter Four is currently under review as; Daniel Devoe; Amy Braun; Thomas Seredynski, Jean Addington (Under Review). *Negative Symptoms and Functioning in Youth at Risk of Psychosis.* Harvard Review of Psychiatry.

Chapter Five is currently being submitted as; Daniel Devoe; K.S. Cadenhead; Barbara Cornblatt, Eric Granholm, Jean Addington. Negative Symptoms Associations with Defeatist Beliefs, Self-Efficacy, and Maladaptive Schemas in Youth At Risk for Psychosis. Behavioral and Cognitive Psychotherapy Journal.

Chapter Six is the conclusion chapter to the thesis.

For each publication the first author (Daniel Devoe) analyzed data, contributed to study design, and drafted the manuscripts. Co-authors assisted in study design, data analysis and critical review of the manuscripts. Published manuscripts are reproduced in this thesis with minor revisions for the purpose of thesis formatting and consistency.

Acknowledgements

First and foremost I would like to thank my supervisor Dr. Jean Addington. I have had the pleasure of working with Jean for over 5 years and would like to express my respect and appreciation for her supervision during my PhD. Jean first gave me the opportunity to join her lab as a clinical rater when I was struggling to find my research area of interest. This opportunity helped me re-discover my passion for mental health research which led me to pursue my PhD with her. Over the course of my PhD Jean has given me more opportunities to both publish and travel to conferences then I would have received with anyone else. Jean has continually pushed me towards excellence at every step of my journey. Watching her productivity and ability to manage so many projects is remarkable and has certainly given me something to hope for and strive for in my future.

I am thankful for my committee members Dr. Eric Granholm, Dr. Gina Dimitropoulos, and Dr. Scott Patten for their guidance, feedback, and support during the course of my PhD. Dr. Eric Granholm took the opportunity to host me for the Mathison Exchange Award, which helped me to develop key skills that aided me in the completion of my thesis. He is the best clinical mentor I have had and during the Regroup Trial he always provided me with thoughtful guidance on how to better help participants. Dr. Dimitropoulos has been an amazing mentor to me throughout my PhD and taught me the value of networking, I always found it so encouraging that she always took every opportunity to introduce me to other mental health professionals. Dr. Scott Patten provided me with sound statistical and methodological advice throughout my PhD. More

importantly he has taken many opportunities to offer me words of encouragement along my journey and has been instrumental in guiding me into my next steps.

I am thankful to the funding agencies and awards that have supported my work including Alberta Innovates Graduate Studentship**,** Queen Elizabeth II Graduate (Doctoral) Scholarship, David Johnston Research Travel Award for Schizophrenia Conference, Dr. S.K. Littman Graduate Award, Graduate Studies International Travel Awards, Mathison Exchange Trainee Award, Profiling Alberta Graduate Students Travel Award, Graeme Bell Graduate Travel Award, Hotchkiss Brain Institute Travel Award, and the Mathison Graduate Scholarship.

Dedication

I would like to dedicate this work to my wife Jennette Devoe, son Everett Devoe, and the unknown baby coming our way. Thank you for putting up with me during my many years of studying. You three will always be the place where I find my joy and my refuge.

Lastly, I would like to dedicate this work to all the youth that I have met that are at clinical high risk for psychosis. Working with these youth over the years has been the fuel that kept me going. I hope that someday we will find a way to better the day to day lives of these youth and find a way to prevent schizophrenia altogether.

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List of Symbols, Abbreviations, and Nomenclature

AMI	Amisulpride
ANOVA	Analysis of Variance
APS	Attenuated Psychotic Symptoms
APSS	Attenuated Positive Symptoms Syndrome
ARMS	At-risk Mental State
BCSS	Brief Core Schema Scale
BIPS	Brief Intermittent Psychotic Syndrome
BNSS	Brief Negative Symptom Scale
BVMT-R	Brief Visuospatial Memory Test-Revised
CAARMS	Comprehensive Assessment of At-Risk Mental State
CBCM	Cognitive-Behavioral Case Management
CBSST	Cognitive Behavioral and Social Skills Training
CBT	Cognitive Behavioral Therapy
CDSS	Calgary Depression Scale for Schizophrenia
CF	Category Fluency
CHR	Clinical High Risk
CI	Confidence Interval
CINAHL	Cumulative Index to Nursing & Allied Health Literature
COPS	Criteria of Psychosis-risk Syndromes
CPT-IP	Continuous Performance Test-Independent Pairs
CRT	Cognitive Remediation Therapy
d	Cohen's d
DHA	Docosahexaenoic Acid
EBM database	Evidence-Based Medicine
EDF40	Penn Emotion Differentiation
Embase	Excerpta Medica Database
EPA	Eicosapentaenoic Acid
ER40	Penn Emotion Recognition
FAM	Family Therapy
FEP	First Episode Psychosis
GF:R	Global Functioning: Role
GF:S	Global Functioning: Social
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRD	Genetic Risk and Deterioration
HVLT-R	Hopkins Verbal Learning Test-Revised immediate recall
I_2	Measure for Heterogeneity
IPI	Integrated Psychological Intervention
k	Kappa
LNS	Letter-Number Span
MATRICS	Measurement and Treatment Research to Improve Cognition in Schizophrenia
MCCB	MATRICS Consensus Cognitive Battery
MD	Mean Difference

MOOSE	Meta-analysis Of Observational Studies in Epidemiology
NAB Mazes	Mazes subtest from the Neuropsychological Assessment Battery
NAC	N-acetylaspartate creatine
NAPLS	North American Prodrome Longitudinal Study
NFI	Needs Focused Intervention
NIMH	National Institute of Mental Health
NMA	Network Meta-analysis
NMDAR	N-methyl-D-aspartate receptor
NOS	Newcastle-Ottawa Scale
NR	Not Reported
OLA	Olanzapine
OME	Omega-3
p	p-values
PANSS	Positive and Negative Syndrome Scale
PINS	Prodromal Interview of Negative Symptoms
PNS	Persistent Negative Symptoms
POPS	Presence of Psychotic Symptoms
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
PUFA	Polyunsaturated Fatty Acid
r	Pearson Correlation Coefficient
RAD-45	Relationships Across Domains
RCTs	Randomized Controlled Trials
RIS	Risperidone
SANS	Scale for the Assessment of Negative Symptoms
SAS-SR	Social Adjustment Scale–Self-Report
SC-BACS	Symbol Coding from the Brief Assessment of Cognition in Schizophrenia
SCOS	The Strauss and Carpenter Prognostic Scale
SD	Standard Deviation
SE	Standard Error
SEM	Standard Error of the Mean
SFS	Social Functioning Scale
SIPS	Structured Interview of Psychosis-Risk Syndromes
SMD	Standardized Mean Difference
SNI	Social Network Index
SOFAS	The Social and Occupational Functioning Assessment Scale
SOPS	Scale of Psychosis Risk Symptoms
SUCRA	Surface Under the Cumulative Ranking Curve
SUP	Supportive Therapy
t	t-values
TASIT	The Awareness of Social Inference Test
TAU	Treatment as Usual
TMT-A	Trail Making Test-Part A

ToM	Theory of Mind
UHR	Ultra-High-Risk
WHOQOL-BREF	The World Health Organization Quality of Life
WMS-III SS	Spatial Span subtest from the Wechsler Memory Scale-III

Epigraph

Research is formalized curiosity. It is poking and prying with a purpose. Zora Neale Hurston

Chapter 1: Introduction to Negative Symptoms in Schizophrenia and Youth at Clinical High Risk for Psychosis

1.1 Introduction

1.2 Negative Symptoms in Schizophrenia

1.2.1 Background & History of Negative Symptoms

Schizophrenia is a serious mental disorder which is characterized by delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behaviour, or negative symptoms.[1] To make the diagnosis of schizophrenia one or more of these symptoms have to be present for a significant portion of time during a one month period with levels in functioning in areas such as occupation, interpersonal relations, or self-care being markedly below the level one achieved prior to the onset of schizophrenia.[1] Historically, the distinction between positive and negative symptoms first emerged from the field of neurology when J.R. Reynolds first described the concept of positive and negative neurological symptoms in 1861 as being either the access of or negative of vital properties.[2] Later, Hughlings Jackson extended on J.R. Reynold's work describing negative symptoms as the "dissolution of neural function" and positive symptoms as resulting from "the release of lower levels from higher inhibitory control".[2] These concepts were later applied within the field of psychiatry with the grouping of symptoms we now associate with schizophrenia first described by Dr. Emile Kraepelin in 1887 using the term dementia praecox with Dr. Eugen Bleuler being the first to use the term schizophrenia in 1911.[3,4] The term positive was coined to describe cognitions or behaviours that were added to or in access in a person with schizophrenia and did not exist before the presence of the disease. Positive psychotic symptoms in schizophrenia consist of altered perceptions such as hallucinations (i.e., changes in auditory, visual, olfactory, gustatory, and tactile sensations or perceptions); delusions (i.e., firmly held

false beliefs that are no based in reality), which may consist of delusions that are persecutory, referential, somatic, religious, or grandiose in nature; thought disorder such as disorganized thinking which may consist of derailment, circumstantial thinking, and tangential thinking; and abnormal motor behaviours such as catatonic behaviour.[1] Antithetically, a negative symptom is used to describe cognitions or behaviours that are absent from a person with a diagnosis of schizophrenia, such as a decrease in motivation.

Historically, early definitions of negative symptoms first emerged from Wilhelm Griesinger in which negative symptoms were described as the absence of will [5] and subsequently described by Emil Kraepelin as a decrease in volition.[6] However, negative symptoms did not gain much research traction until 1974 when Will Carpenter and colleagues advocated that positive and negative symptoms should be separated for research purposes.[7] This was further supported by the emergence of several scales in the late 1900's, which were instrumental in the development of research into negative symptoms. First, the development of the Brief Psychiatric Rating Scale,[8] followed by the Positive and Negative Syndrome Scale (PANSS),[9] and subsequently by the Scale for the Assessment of Negative Symptoms (SANS).[10] In 1988, differentiating between enduring negative symptoms and transient negative symptoms in patients with schizophrenia led to the emergence of the deficit syndrome.[11] Deficit syndrome is defined as, "a disease entity characterized by the presence of primary enduring negative symptoms".[12] Succinctly, to meet criteria for deficit syndrome, a patient must have a minimum of two of six negative symptoms (i.e., restricted affect, diminished emotional range, poverty of speech, decreased interests, diminished sense of purpose,

diminished social drive) which have been present for the past year, are considered primary negative symptoms, and the patient must meet the DSM criteria for schizophrenia.[13] The biological correlates of negative symptoms are best understood by comparing deficit syndrome and non-deficit syndrome patients. In imaging studies patients with deficit syndrome have been shown to have smaller gray matter volumes in the superior prefrontal, superior temporal, and middle temporal gyri [14]. Another study showed that patients with deficit syndrome had decreased activation in the thalamus compared to controls and non-deficit patients.[15] In a neurochemical imaging study deficit patients had lower N-acetylaspartate creatine (NAC) than non-deficit patients.[16] In a metabolic study, deficit patients had higher interleukin-6 concentrations compared to control and non-deficit patients.[17] Lastly, in a meta-analysis deficit patients had greater global cognitive impairments, social cognition, and performed poorer on olfaction tests than non-deficit patients.[18] However, to date our understanding regarding the biological correlates of negative symptoms remains limited to a handful of studies on negative symptoms in schizophrenia and has resulted in poor treatment designs for negative symptoms.[19]

Various mechanisms have been implicated in the development of negative symptoms, that include neurotransmitters, brain structure and function, inflammation, and cognitive, environmental, and psychosocial factors.[20] From a neurotransmitter perspective, changes in neurotransmitter systems may predispose an individual to develop negative symptoms, such as a decrease in hypofunctionality of dopamine D1 receptor neurotransmission in the prefrontal cortex.[21] From a structural perspective, greater negative symptoms in schizophrenia have been shown to be associated with

tissue reduction in the frontal lobes and increased grey matter in the right posterior superior temporal gyrus.[22] From a psychosocial mechanism perspective, some have postulated that negative symptoms arise from distress beyond an individual's ability to cope where both over exposure to negative environmental and social stimuli lead to negative symptoms by causing various psychological systems to shutdown.[23] Thus, negative symptoms appear to be multifactorial in nature.

1.2.2 Brief Overview of Treatment and Negative Symptoms in Schizophrenia

The largest meta-analysis to date was a meta-analysis of 168 RCTs that examined the impact of treatment on negative symptoms in schizophrenia.[24] This review showed that many treatments did reduce negative symptoms including second generation antipsychotics (Effect Size: 0.579), antidepressants (Effect Size: 0.349), and psychosocial interventions (Effect Size: 0.396). According to the review the most effective treatment was second generation antipsychotics. First generation antipsychotics (Effect Size: 0.531) and brain stimulation (Effect Size: 0.228) had no statistically significant effect on negative symptoms. Even though many studies in the review decreased negative symptoms, the authors concluded that almost no studies to date were designed to target negative symptoms nor used the required design for efficacy. Furthermore, they contended that even for treatments that were significant, most were not clinically significant as measured on Clinical Global Impression Severity Scale. Unfortunately, the review did not look at studies that specifically targeted negative symptoms as a primary outcome and this may have led to a potential bias in the meta-analytical results. Another issue that arises that the above review did not

address was the pseudospecificity problem. That is that second generation antipsychotics look like they improve the negative symptoms of patients who enter into a clinical trial when positive symptoms may be at their peak. Since positive symptoms can intensify negative symptoms the improvement in negative symptoms in a clinical trial geared towards positive symptoms should be interpreted with caution, especially if the positive and negative symptoms improve at the same time.

More recent systematic reviews and meta-analyses have offered more optimistic and alternative perspectives on the treatment of negative symptoms in schizophrenia when compared to the previous review. Two recent reviews looked at the impact of mind-body and physical exercise on negative symptoms in schizophrenia and found that physical exercise could be a promising intervention for negative symptoms in schizophrenia.[25,26] A third review examining psychological and psychosocial interventions for negative symptoms concluded that cognitive-behavioural therapy, social skills training, and music therapy all significantly reduced negative symptoms when compared to treatment as usual.[27] Finally, another area that has garnered a lot of interested in recent years has been NMDAR antagonists (phencyclidine and ketamine) which can induce cognitive and behavioral changes comparable to positive and negative symptoms in patients with schizophrenia, thus formulating the NMDAR modulator postulate.[28-30] However, the NMDAR modulator literature to date has demonstrated mixed results in regards to improving negative symptoms for those with schizophrenia.[31]

1.2.3 Consensus on Negative Symptoms in Schizophrenia

Due to the slow advancement of negative symptom research relative to positive symptoms, the NIMH-MATRICS consensus group was formed [(National Institute of Mental Health (NIMH) - Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS)].[32,33] The group succeeded in a consensus of eleven points regarding negative symptoms that clinicians and researchers should consider. The main points advocated that negative symptoms are distinct from positive symptoms and cognitive deficits and thus clinical trials should target negative symptoms specifically as a primary outcome. Furthermore, persistent and clinically meaningful negative symptoms generally remain untreated in a large amount of cases. Other notable points that emerged from NIMH-MATRICS consensus on negative symptoms were that the design of future trials targeting negative symptoms should take into account a variety of methodical considerations including a co-primary measure of functional improvement, optimal duration, investigation into interventions and agents that could have broad spectrum implications for both positive and negative symptoms, and addressing the strengths and weaknesses of available instruments for measuring negative symptoms.[33]

1.2.4 Primary and Secondary Negative Symptoms

To date, many studies in schizophrenia do not differentiate between primary negative symptoms and secondary negative symptoms.[33] Primary negative symptoms are negative symptoms that are associated with the pathophysiological mechanisms of schizophrenia, meaning that they are not secondary in nature nor related to negative symptoms that might emerge from a comorbid diagnosis such as depression (secondary negative symptoms). Common secondary negative symptoms are derived

from depression, drug-induced akinesia, social deprivation, and chronic disease.[34] The distinction between primary and secondary negative symptoms is an important difference to make, especially for implementing treatment and determining efficacy. The distinction between patients with primary negative symptoms versus secondary negative symptoms can be detected with good reliability.[35]

1.3 Negative Symptoms in Populations at Clinical High Risk of Psychosis

1.3.1 The Clinical High Risk State

In recent years, the field of early recognition of psychosis has become well-recognized in schizophrenia research. Most early recognition research has focused on attenuated positive psychotic symptoms, which includes unusual thoughts, suspiciousness, grandiosity, perceptual abnormalities, and disorganized speech. Well-established criteria have emerged to delineate those who are at clinical high risk (CHR) for developing psychosis. Meeting criteria for being at CHR for psychosis can be established using valid structured interviews such as the Structured Interview of Psychosis-Risk Syndromes (SIPS)[36] or the Comprehensive Assessment of At-Risk Mental State (CAARMS).[37] The Criteria of Prodromal Syndromes (COPS) is based on the SIPS, which can be divided into three distinct prodromal syndromes: attenuated positive symptoms syndrome (APSS), genetic risk and deterioration (GRD) syndrome, and the brief intermittent psychotic syndrome (BIPS) (McGlashan et al.,2010). Individuals who meet APSS criteria typically experience attenuated psychotic symptoms that are below the threshold of full-blown psychotic symptoms (rated a six on the SIPS). Consequently, CHR individuals with predominantly negative symptoms and less severe attenuated positive symptoms are not necessarily perceived as needing treatment.[38]

Thus, most cohort and interventional studies examining those at CHR for psychosis have focused on the prevention of transition to psychosis or the reduction of attenuated psychotic symptoms and the associations of attenuated psychotic symptoms, while largely ignoring negative symptoms.[39]

1.3.2 Negative Symptoms in the Clinical High Risk State

Researchers have described negative symptoms as being non pathognomonic in that negative symptom have been observed not just in in schizophrenia-spectrum disorders, but in other disorders including bipolar disorder, major depressive disorder, and autism spectrum disorder, as well as in the general population.[40] In addition, those at CHR for psychosis frequently present with a wide range of negative symptoms such as flat affect, alogia, anhedonia, avolition, emotional withdrawal, and asocialty.[41] Furthermore, CHR youth often demonstrate persistent and significant negative symptoms, which have been reported to be predictive of transition to a psychotic disorder.[42-46] Moreover, negative symptoms have been shown to reduce quality of life and impact long-term outcomes in CHR individuals, [47-50] nevertheless they remain undertreated. As previously stated, even in schizophrenia, treatment development for negative symptoms has remained slow.[51] There is a clear need for interventions for treating a range of symptoms in CHR youth,[52] including negative symptoms. This has led to renewed interest in understanding the determinants of negative symptoms [53] and designing interventions to decrease the burden of negative symptoms in CHR youth.[30,54] However, approximately only 20% of CHR youth transition to a psychotic disorder and thus it is important to reconsider and re-examine negative symptoms in the context of

the CHR population and not rely on the current models of negative symptoms presented in schizophrenia research.

For the purpose of this thesis a manuscript-based approach was undertaken. Each manuscript is provided from Chapters 2-5 with Chapter 6 providing an overall conclusion. Focusing on negative symptoms in four manuscripts will expand the knowledge base on negative symptoms in CHR and aid in knowledge translation.

Chapter 2: Negative Symptom Interventions in Youth at Risk of Psychosis: A Systematic Review and Network Meta-Analysis

2.1 Preface

Research presented as part of this chapter are published as; Daniel Devoe; Aaron Peterson; Jean Addington (2017). *Negative Symptom Interventions in Youth at Risk of Psychosis: A Systematic Review and Network Meta-Analysis.* Schizophrenia Bulletin.

An erratum to this manuscript is provided in Appendix A.

Author Contributions: DD wrote the initial manuscript and conducted the meta-analysis. JA was involved in writing the subsequent drafts of the manuscript. AP assisted in data extraction and quality assessment. All authors listed were involved in the study design and have contributed to and approved the final manuscript.

The only alterations made to this publication were for thesis formatting.

2.2 Abstract

Objective: Youth at clinical high risk (CHR) for psychosis often demonstrate significant negative symptoms, which have been reported to be predictive of conversion to psychosis and a reduced quality of life but treatment options for negative symptoms remain inadequate. Therefore, we conducted a systematic review and network meta-analysis of all intervention studies examining negative symptom outcomes in youth at CHR for psychosis.

Method: The authors searched PsycINFO, Medline, Embase, CINAHL, and EBM from inception to December 2016. Studies were selected if they included any intervention that reported follow-up negative symptoms in youth at CHR for psychosis. Treatment comparisons were evaluated using both pairwise and network meta-analyses. Due to the differences in negative symptom scales the effect sizes were reported as the standardized mean difference (SMD).

Results: Of 3,027 citations, 32 studies met our inclusion criteria, including a total of 2,463 CHR participants. N-methyl-D-aspartate-receptor (NMDAR) modulators trended towards a significant reduction in negative symptoms compared to placebo (SMD, -0.54; 95% CI, -1.09 to 0.02; I_2 = 0%, P = 0.06). In respective order of descending effectiveness as per the treatment hierarchy, NMDAR modulators were more effective than family therapy, needs based interventions, risperidone, amisulpride, cognitive behavioral therapy, omega-3, olanzapine, supportive therapy, and integrated psychological interventions.

Conclusions: Although this review demonstrated small-large effect sizes between interventions and a reduction in negative symptoms many relevant studies had small

samples and the majority were not designed to target negative symptoms, thus reducing their clinical importance with respect to negative symptoms.

2.3 Introduction

Attenuated psychotic symptoms have been the primary focus in individuals at clinical high risk (CHR) for psychosis both for meeting inclusion criteria using either the Structured Interview of Psychosis-Risk Syndromes (SIPS)[36] or the Comprehensive Assessment of At-Risk Mental State (CAARMS)[37] and for subsequent conversion to a full-blown psychotic disorder.[53] Consequently, CHR individuals with predominantly negative symptoms and less severe attenuated positive symptoms are not necessarily perceived as needing treatment.[38] Thus, interventional studies examining those at CHR for psychosis have predominately focused on the prevention of conversion or the reduction of attenuated psychotic symptoms, while largely ignoring negative symptoms.[39] However, evidence suggests that negative symptoms in the CHR state may provide insight into underlying pathophysiological mechanisms in schizophrenia and lead to effective interventions.[55,56]

Youth at CHR for psychosis frequently present with a wide range of negative symptoms such as flat affect, alogia, anhedonia, avolition, emotional withdrawal, difficulty in abstract thinking, and deterioration in role functioning.[41] Furthermore, CHR youth often demonstrate persistent and significant negative symptoms, which have been reported to be predictive of conversion to a psychotic disorder.[42-46] Moreover, negative symptoms have been shown to reduce quality of life and impact long-term outcomes in CHR individuals,[47-50] nevertheless they remain undertreated. In fact, even in schizophrenia, treatment development for negative symptoms has remained slow.[51] There is a clear need for interventions for treating a range of symptoms in CHR youth,[52]

including negative symptoms. This has led to renewed interest in understanding the determinants of negative symptoms[53] and designing interventions to decrease the burden of negative symptoms in CHR youth.[30,54]

A previous traditional meta-analysis examined the effects of different interventions on negative symptoms as a secondary outcome reported in nine studies in a search performed in 2011 and only found a difference in negative symptoms in a single omega-3 trial considered to be of low quality.[39,57] Since then interventional studies in CHR samples have increased substantially and are comprised of newer approaches such as N-methyl-D-aspartate receptor (NMDAR) modulator interventions (glycine and D-serine), cognitive remediation therapy (CRT), and family therapy. Our review expands on the previous review, by including more than a threefold increase in interventional studies and the impact on negative symptoms as a primary outcome, not only in traditional pairwise meta-analyses, but in paired pre/post non-randomized controlled studies meta-analyses and finally a network meta-analysis (NMA). The NMA allowed for indirect comparisons between treatment arms that have not been compared before (e.g. omega-3 to glycine) that used a common comparator (e.g. placebo). By including additional studies, new interventions, pre/post interventional studies, and indirect evidence, the evidence base on negative symptom interventions in CHR youth will be expanded.

2.4 Method

2.4.1 Protocol

This systematic review and NMA was conducted according to a pre-specified protocol (PROSPERO [International Prospective Register of Systematic Reviews]

number: CRD42016049319) and reported in accordance with MOOSE and PRISMA guidelines.[58-61] PRISMA checklists for both pairwise and network meta-analyses are provided in Supplementary Material 1.[62,63]

2.4.2 Search Strategy

The authors conducted an electronic database search of PsycINFO, Medline, Embase, CINAHL, and EBM from inception to December 2016. Full search details are shown in Supplementary Material 2. Each reviewer (A.P. and D.D.) independently performed title and abstract screening, and the full text of any study considered relevant according to the selection criteria was retrieved for detailed review. In addition, a Google Scholar search was conducted using the key words “psychosis risk” and “treatment” and both The International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/) and the Clinicaltrials.gov registry were searched using the terms “psychosis” and “risk”. Finally, reference lists of included articles were hand-searched for relevant citations.

2.4.3 Selection Criteria

Two reviewers (A.P. and D.D.) independently assessed the full text of each potentially relevant study for inclusion. Studies that met the following eligibility criteria were selected: (1) studies including participants at risk of psychosis meeting established criteria for CHR for psychosis, the attenuated psychosis syndrome (APS), the at-risk mental state (ARMS), ultra-high-risk (UHR), or schizotypy; (2) studies including observational interventions or experimental treatments; (3) studies reporting follow-up negative symptom scores reported using the Positive and Negative Syndrome Scale (PANSS),[64] the Scale for the Assessment of Negative Symptoms (SANS),[10] the Scale of

Prodromal Symptoms (SOPS),[65] or the Comprehensive Assessment of At-Risk Mental States (CAARMS),[66] and (4) studies reporting a mean age between 12-30. Studies were not excluded based on languages. Case reports, review articles, editorials, non-intervention studies, and articles with overlapping datasets were excluded. Disagreements were resolved by a third author (J.A.).

2.4.4 Data Extraction

All data were extracted in duplicate and included study characteristics (author, publication year, country, study design, sample size, and negative symptom scale), participant details (number of CHR participants, mean ± *SD* age, number of males / percent male), and treatment characteristics (intervention, control, treatment duration, and negative symptom results). The following clinical outcome data were extracted: (1) mean ± *SD* negative symptom scores at follow-up and baseline, (2) sample size per treatment group, and (3) paired pre/post negative symptom scores for non-randomized controlled studies with the *P* or *t* value of change in negative symptom scores. If articles only provided confidence intervals or standard error, a standard deviation was obtained using the methods described in the Cochrane Handbook.[67] Additional data was obtained by contacting corresponding authors, accessing ClinicalTrials.gov, obtaining follow-up articles, and extracting data from graphical format using GraphClick software.[68] Articles published in languages other than English were translated using the Google Translator Toolkit.

2.4.5 Risk-of-Bias Assessment

For randomized studies included in the pairwise meta-analysis, risk of bias was evaluated using the Cochrane Collaboration's tool for assessing risk of bias.[67] To

evaluate the quality of evidence associated with comparisons in the NMA colored edges (Green = Low Risk, Yellow= Unclear Risk, Red= High Risk) according to risk of bias for blinding of outcome assessments was estimated as the level of bias in the majority of the trials and weighted according to the number of studies in each comparison. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to evaluate the quality of evidence associated with the results in the NMA and the Newcastle-Ottawa Scale (NOS) criteria was applied to non-randomized studies.[69,70] Quality assessment did not influence the decision to include studies in the meta-analyses.

2.4.6 Data Synthesis and Analysis

Due to the differences in negative symptom scales the principal summary measures used across the majority of meta-analyses (i.e. pairwise, paired non-randomized controlled studies, and network meta-analyses) were effect sizes calculated as Hedges *g.* Hedges *g* was reported as the standardized mean difference (SMD) of negative symptom scores at follow-up.[71] Glycine and D-serine (herein: NMDAR modulators) are both amino acids that serve as neuromodulators in the brain by acting as a coagonist on the NMDAR in combination with glutamate,[29,72] thus both were combined in pairwise and network meta-analyses. Treatment as usual, community care, monitoring, and needs focused interventions were pooled as needs-based interventions in the meta-analyses due to similarities in design. Finally, due to expected differences between studies due to study design, CHR criteria, and the different treatment strategies, all results were combined using random-effects models.

For the primary analyses, direct treatment effects on negative symptoms from interventions (e.g. two studies comparing omega-3 to placebo) were combined using a pairwise random-effects model by DerSimonian and Laird.[73] If negative symptom scores were rated on the same scale the pooled mean difference (MD) was reported instead of the SMD. Thus, the likelihood of a reduction in negative symptoms in CHR youth who received a similar intervention was compared to a control. Direct treatment comparisons and risk of bias were analyzed using Review Manager 5.[74] Paired pre/post non-randomized controlled studies (e.g. three aripiprazole studies reporting paired sample results) meta-analyses were analyzed using the Comprehensive Meta-Analysis Software.[73] Essentially, paired sample observations were pooled, thus measuring negative symptoms before and after receiving an intervention in the absence of a control.[75,76]

For the secondary analysis, RCTs treatment effects between individual intervention arms were evaluated using a random-effects multivariate NMA (greater details are provided for the NMA in Supplementary Material 3) assuming consistency and a common heterogeneity across all comparisons in the network model.[77,78] The NMA allowed for indirect comparisons between treatment arms that have not been compared before (e.g. omega-3 to glycine to antipsychotics) that used a common comparator (e.g. placebo) by integrating direct evidence (e.g. an existing study comparing omega-3 to placebo).[79] Transitivity is a critical assumption in a NMA, which assumes that comparisons in the network model are consistent (similar effect modifiers such as age across all interventions).[80-82] Simply put, whether it was equally likely that any CHR youth in the network could not be contraindicated to any of the treatments in

the network,[83] due to this schizotypy studies were excluded from the NMA. Thus, an inconsistency plot assuming loop-specific heterogeneity was produced to determine what might be important sources of inconsistency between direct and indirect evidence.[84-87] In addition, baseline characteristics (age, CHR criteria) that might modify the treatment effect were restricted using an a priori inclusion criteria to prevent inconsistencies from being introduced into the model. Surface under the cumulative ranking curve (SUCRA) plots were visually inspected to determine the most effective interventions compared to a superior hypothetical treatment, the faster a curve approaches one, the more probable it will be more effective.[81,84] Publication bias was assessed using a network comparison-adjusted funnel plot.[84] Data in the NMA were analyzed using Stata, version 13.1 (StataCorp LP). The graphical toolset in Stata called “networkplot” was utilized to produce graphical representations of the network evidence.[84]

Statistical heterogeneity was quantified using the I^2 statistic with an $I^2 \geq 50\%$ indicating substantial heterogeneity and an $I^2 \geq 75\%$ indicating considerable heterogeneity. Inter-rater reliability for title and abstract screening was calculated using the kappa statistic. All SMDs (effect sizes) with a $P < .05$ were considered significant and as a general guide SMDs of 0.2 represented a small effect, 0.5 a medium effect, and 0.8 a large effect.[88]

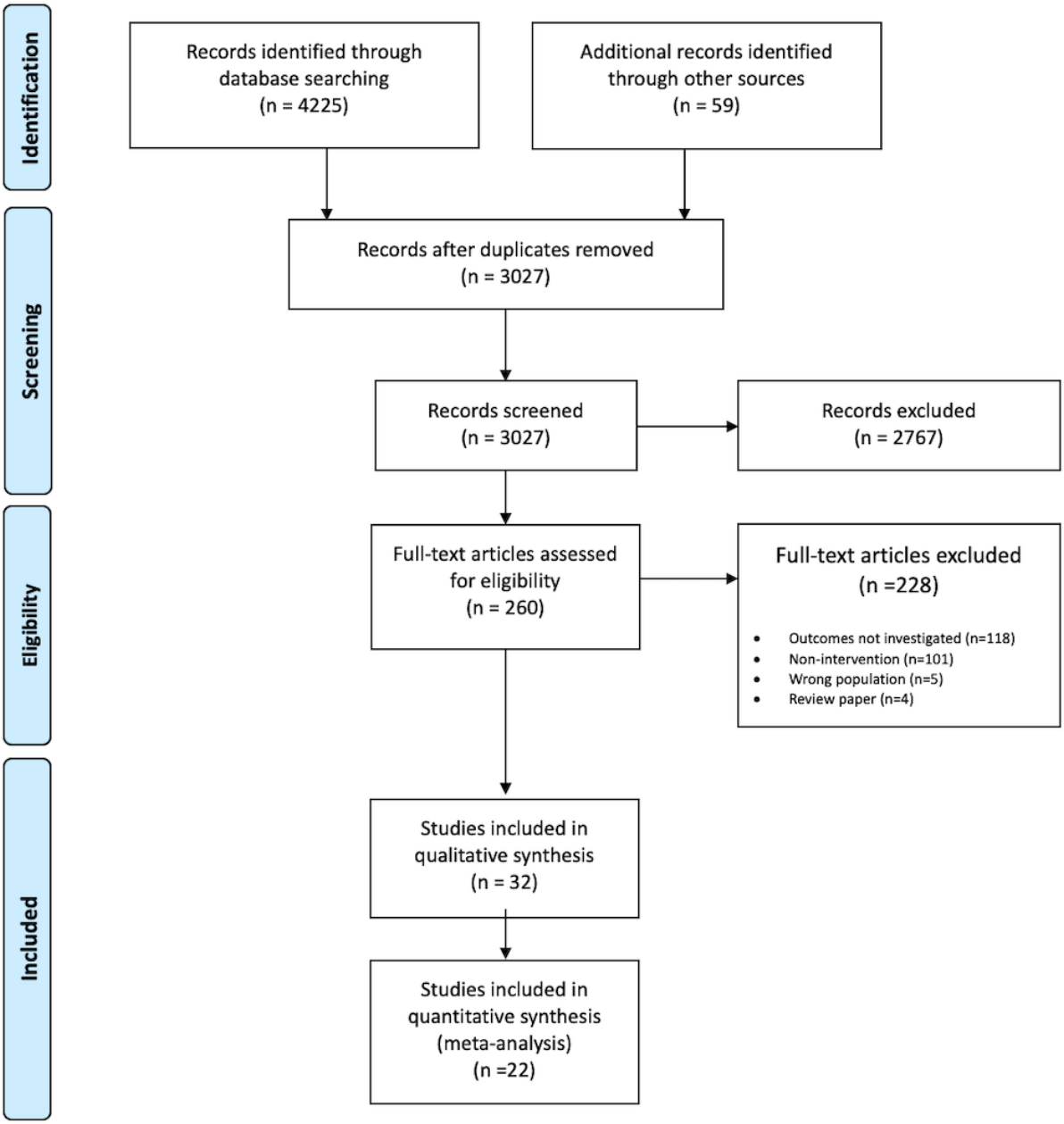
2.5 Results

2.5.1 Search Yield

The search strategy generated 3,027 unique citations; 2,767 citations were excluded after reviewing title and abstract. The study eligibility agreement between

reviewers for abstract and title screening was high (κ = 0.91). A total of 260 articles were retrieved for full-text review (figure 2.1). Of these, 32 primary studies were eligible for inclusion in our systematic review of which 22 were included in the meta-analyses. Reasons for exclusion included outcomes of interest not reported in the article (*n* = 118), non-intervention study (*n* = 101), wrong population (*n* = 5), and review paper (*n* = 4; figure 1). Among the 32 included studies, 13 were non-randomized or non-controlled observational studies and 19 were RCTs. Additional data for 9 studies was acquired from the corresponding authors.

Figure 2.1 PRISMA flow diagram of systematic search and included studies



PRISMA flow diagram of systematic search and included studies.

2.5.2 Study and Participant Characteristics

Characteristics of the 32 studies included in the systematic review are outlined in Table 1. Of the 32 studies, 15 studies were conducted in North America,[72,89-101] 9 in Europe,[102-110] 4 in Australia,[111-114] and 4 in Asia.[115-118] Sixteen studies measured negative symptoms with the SOPS, PANSS (*N* = 10), SANS (*N* = 5), and the CAARMS (*N* = 3). The number of CHR participants ranged from 5 to 304, for a total of 2,463 CHR participants. The mean age was 20.3 years (range = 15.6–27.2 y) and 1,348 (54.7%) were male (range = 29–75%).

Table 2.1 Details of Included Studies (N=32)

Author + Year	Country	Study Design	Intervention (CHR n)	Control (CHR n)	Included in Analysis	Sample Size	Treatment Duration (weeks)	CHR Patients			Negative Symptom Results	Negative Symptom Measure
								N	Age (*M*, SD)	Male (N, %)		
Cognitive Behavioral Therapy												
Addington (2011)	Canada	RCT	CBT (27)	Supportive therapy (24)	NMA + Pairwise	51	24	51	21.0(NR)	36(70)	Reduced negative symptoms in both groups	SOPS
Fusar (2015)	UK	Naturalistic	CBT (59)	CBT + AP (31) / CBT + AD (27) / CBT + AP + AD (33)	Not included in meta-analysis	258	NR	258	22.9(4.5)	147(57)	Patients with more severe negative symptoms preferred antidepressants	CAARMS
Ising (2016)	Netherlands	RCT	CBT + TAU (95)	TAU (101)	NMA + Pairwise	196	24	196	22.7(NR)	97(49)	No significant reduction in negative symptoms in both groups	CAARMS
Family Based Therapy												
McFarlane (2015)	USA	Regression discontinuity design$_{\chi}$	Family-aided Assertive Community Treatment (205)	Community care (NA)	Pre/Post Analysis	337	104	205	16.4(3.3)	116(57)	Significant reduction in negative symptoms in treatment group	SOPS
Landa (2016)	USA	Open label	Group-and-family-based-CBT (6)	None (NA)	Pre/Post Analysis	6	15	6	19.5(1.5)	2(33)	Reduced negative symptoms	CAARMS, PANSS
Miklowitz (2014)	USA + Canada	RCT	Family-focused therapy (66)	Enhanced care (63)	NMA	129	24	129	17.4(4.1)	74(57)	Reduced negative symptoms in both groups$_{\ddagger}$	SOPS
Omega-3												

Author + Year	Country	Study Design	Intervention (CHR n)	Control (CHR n)	Included in Analysis	Sample Size	Treatment Duration (weeks)	CHR Patients			Negative Symptom Results	Negative Symptom Measure
								N	Age (*M*, SD)	Male (N, %)		
McGorry (2017)	Australia	RCT	Omega-3 ω-3 PUFA (1.4 g/day) + CBCM (153)	Placebo + CBCM (151)	NMA + Pairwise	304	24	304	19.1(4.6)	139(46)	No reduction in negative symptoms	SANS
Amminger (2010)	Austria	RCT	Omega-3 PUFA (1.2 g/day) (41)	Placebo (40)	NMA + Pairwise	81	12	81	16.4(NR)	27(33)	Reduced negative symptoms in intervention group	PANSS
Cadenhead (2017)	USA + Canada	RCT	Omega-3 (740 mg of EPA and 400 mg of DHA/day) (65)	Placebo (62)	NMA + Pairwise	127	52	127	18.8(NR)	71(56)	No significant difference in negative symptoms at follow-up	SOPS
Cognitive Remediation												
Choi (2016)	USA	RCT	CRT (30)	Tablet computer games (32)	Pairwise	62	8	62	18.35(NR)	32(51)	No reduction in negative symptoms in either group‡	SOPS
Urben (2012)	Switzerland	RCT	CRT (7)	Computer games (5)	Not included in meta-analysis	32	8	12	15.6(NR)	18(56)	No reduction in negative symptoms	PANSS
Hooker (2014)	USA	Open label	CRT (14)	Computer games (NA)	Not included in meta-analysis	28	8	14	21.9(4.2)	7(50)	No reduction in negative symptoms	SOPS
Loewy (2016)	USA	RCT	CRT (50)	Computer games (33)	Pairwise	83	8	83	18.2(NR)	42(51)	No significant reduction in negative symptoms in both groups	SOPS
Piskulic (2015)	Canada	RCT	CRT (23)	Computer games (20)	Pairwise	32	12	32	18.61(NR)	21(66)	No reduction in negative symptoms in either group‡	SOPS

Author + Year	Country	Study Design	Intervention (CHR n)	Control (CHR n)	Included in Analysis	Sample Size	Treatment Duration (weeks)	CHR Patients			Negative Symptom Results	Negative Symptom Measure
								N	Age (*M*, SD)	Male (N, %)		
Rauchensteiner (2009)	Germany	Open label	CRT (10)	None (NA)	Not included in meta-analysis	26	4	10	27.2(5.3)	7(70)	No reduction in negative symptoms	PANSS
Integrated Psychological Therapies												
Nordentoft (2006)	Denmark	RCT	IPI (NA)	Standard treatment (NA)	Not included in meta-analysis	79	104	79 α	24.9(4.9)	53 (67)	Reduced negative symptoms in intervention group	SANS
Wessels (2015)	Germany β	RCT	IPI (53)	Supportive therapy (52)	NMA	128	52	128	26.0(NR)	81(63)	Reduced negative symptoms in both groups	PANSS
N-methyl-D-aspartate-receptor (NMDAR) modulators												
Kantrowitz (2016)	USA	RCT	D-serine (60 mg/kg) (20)	Placebo (24)	NMA + Pairwise	35	16	35	19.5(NR)	23(65)	Reduced negative symptoms in intervention group	SOPS
Woods (2013)	USA	Open label δ	Glycine (0.8 g/kg/d) (10)	None (NA)	Not included in meta-analysis	10	8	10	17.3(3.3)	7(70)	Medium effect sizes from treatment for negative symptoms	SOPS
Woods (2013)	USA	RCT δ	Glycine (0.8 g/kg/d) (4)	Placebo (4)	NMA + Pairwise	8	24	8	15.9(NR)	6(75)	Medium effect sizes from treatment for negative symptoms	SOPS
Antipsychotics												
Aripiprazole												
Kobayashi (2009)	Japan	Open label	Aripiprazole (mean range dose 7.1-10.7 mg/day) (36)	None (NA)	Pre/Post Analysis	36	8	36	23.4(5.6)	15(42)	Significant reduction in negative symptoms	SOPS

Author + Year	Country	Study Design	Intervention (CHR n)	Control (CHR n)	Included in Analysis	Sample Size	Treatment Duration (weeks)	CHR Patients			Negative Symptom Results	Negative Symptom Measure
								N	Age (*M*, SD)	Male (N, %)		
											compared to baseline	
Liu (2012)	Taiwan	Open label	Aripiprazole (3.75 mg/d increased to 15 mg/d) (10)	Antipsychotic-short-exposure patients (NA)	Pre/Post Analysis	31	4	11	21.4(NR)	6(54)	No reduction in negative symptoms in both groups	PANSS
Woods (2007)	USA	Open label	Aripiprazole (5-30mg/day) (15)	None (NA)	Pre/Post Analysis	15	8	15	17.1(5.5)	8(53)	Significant reduction in negative symptoms compared to baseline	SOPS
Risperidone												
Cannon (2002)	Finland	Open Label	Risperidone (1.0 - 1.8 mg/day) (5)	None (NA)	Not included in meta-analysis	16	12	5	15.6(0.8)	3(60)	No significant reduction in social withdrawal	PANNS
McGorry (2002)	Australia	RCT	Risperidone (mean dose 1.3mg/d) + CBT (31)	NBI (28)	NMA + Pairwise	59	24	59	20(4.0)	34(58)	No significant reduction in negative symptoms in both groups	SANS
McGorry (2013)	Australia ŷ	RCT	Risperidone (0.5mg/d increased to 2mg/d) + CBT (43) or CBT + Placebo (44)	Supportive Therapy + Placebo (28) or Monitoring (78)	NMA + Pairwise	193	52	193	18.1(NR)	81(42)	Negative symptoms improved in all three groups	SANS
Other Antipsychotics												
McGlashan (2006)	USA + Canada	RCT	Olanzapine (5-15 mg/day) (31)	Placebo (29)	NMA + Pairwise	60	52	60	17.7(NR)	39(65)	No reduction in negative symptoms in intervention group	SOPS, PANSS
Ruhrmann (2007)	Germany	RCT	Amisulpride (mean dose 118.7mg/d) + NFI (65)	NFI (59)	NMA	124	12	124	25.6(6.3)	70(57)	Reduced negative symptoms in intervention group	PANSS

Author + Year	Country	Study Design	Intervention (CHR n)	Control (CHR n)	Included in Analysis	Sample Size	Treatment Duration (weeks)	CHR Patients			Negative Symptom Results	Negative Symptom Measure
								N	Age (*M*, SD)	Male (N, %)		
Tsujino (2013)	Japan	Open Label	Perospirone (mean dose 4.0 mg daily increased to 10.2mg daily) (11)	None (NA)	Not included in meta-analysis	11	26	11	26.7(6.5)	4(36)	No significant reduction in negative symptoms	SOPS
Washida (2013)	Japan	Open Label	Second Generation Anti-psychotics (17)	None (NA)	Not included in meta-analysis	61	12	17	23.7(4.4)	5(29)	CHR group showed major improvement in negative symptoms	PANNS
Woods (2017)	USA	RCT	Ziprasidone (20-160mg/d) (24)	Placebo (27)	NMA	50	24	50	22.25(NR)	32(64)	No significant difference in negative symptoms at follow-up	SOPS
Mood Stabilizers												
Berger (2008)	Australia	Open Label	Low-dose lithium (450mg/day) (25)	Monitoring (78)	Not included in meta-analysis	103	52	103	19.0(NR)	45(32)	No reduction in negative symptoms in either group‡	SANS

Abbreviations: CAARMS= Comprehensive assessment of at-risk mental states; CBCM= Cognitive-behavioral case management; CBT= cognitive behavioral therapy; CRT = cognitive remediation therapy; DHA = docosahexaenoic acid; EPA= eicosapentaenoic acid; IPI= Integrated psychological intervention; NFI = Needs focused intervention; NR= not reported; PANSS= Positive and negative syndrome scale; PUFA = polyunsaturated fatty acid; SANS= Scale for the assessment of negative symptoms; SOPS= Scale *of* prodromal symptoms***;*** TAU = treatment as usual

‡ Negative symptom data obtained from corresponding authors

Ÿ Multinational trial: Australia, Switzerland, Germany, Denmark, Hong Kong, Austria, and Singapore.

α Sample contained participants at risk of transition to psychosis based on schizotypy

β Article was translated from German to English using the Google Translator Kit

χ Risk-based Allocation Design

δ Two studies were reported in one publication

2.5.3 Features of Treatment Interventions and Controls

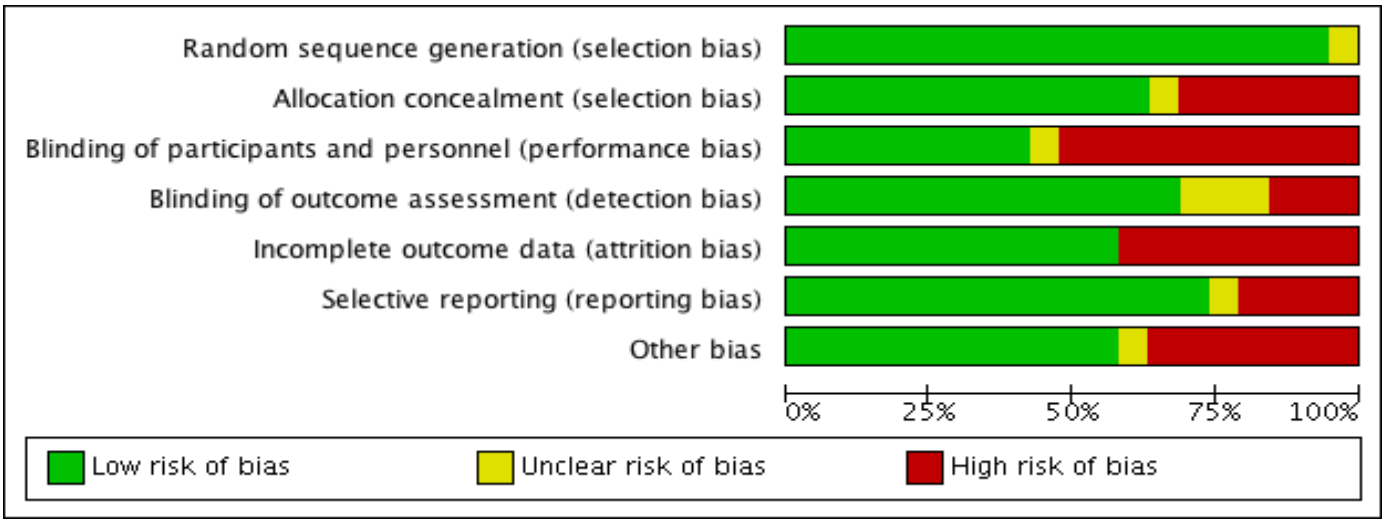
The mean treatment duration was 26.3 weeks (range = 4–104 wks.). The nature of the interventions varied greatly between studies; cognitive remediation therapy (*N* = 6), cognitive behavioral therapy (*N* = 3), aripiprazole (*N* = 3), family based treatments (*N* = 3), NMDAR modulators (*N* = 3), risperidone (*N* = 3), omega-3 (*N* = 3), integrated psychological intervention (*N* = 2), amisulpride (*N* = 1), olanzapine (*N* = 1), low-dose lithium (*N* = 1), ziprasidone (*N* = 1), perospirone (*N* = 1), and second generation antipsychotics (*N* = 1). The control conditions varied as well; placebo (*N* = 7), computer games (*N* = 5), needs based interventions (*N* = 5), supportive therapy (*N* = 3), community care (*N* = 2), antipsychotic short-term exposure patients (*N* = 1), and combination therapies (*N* = 1) . Eight studies did not use a control group. Seven interventions included additional participants (*n* = 308) that were not at CHR and consequently these participants were excluded from the current analyses.

2.5.4 Risk-of-Bias Assessment

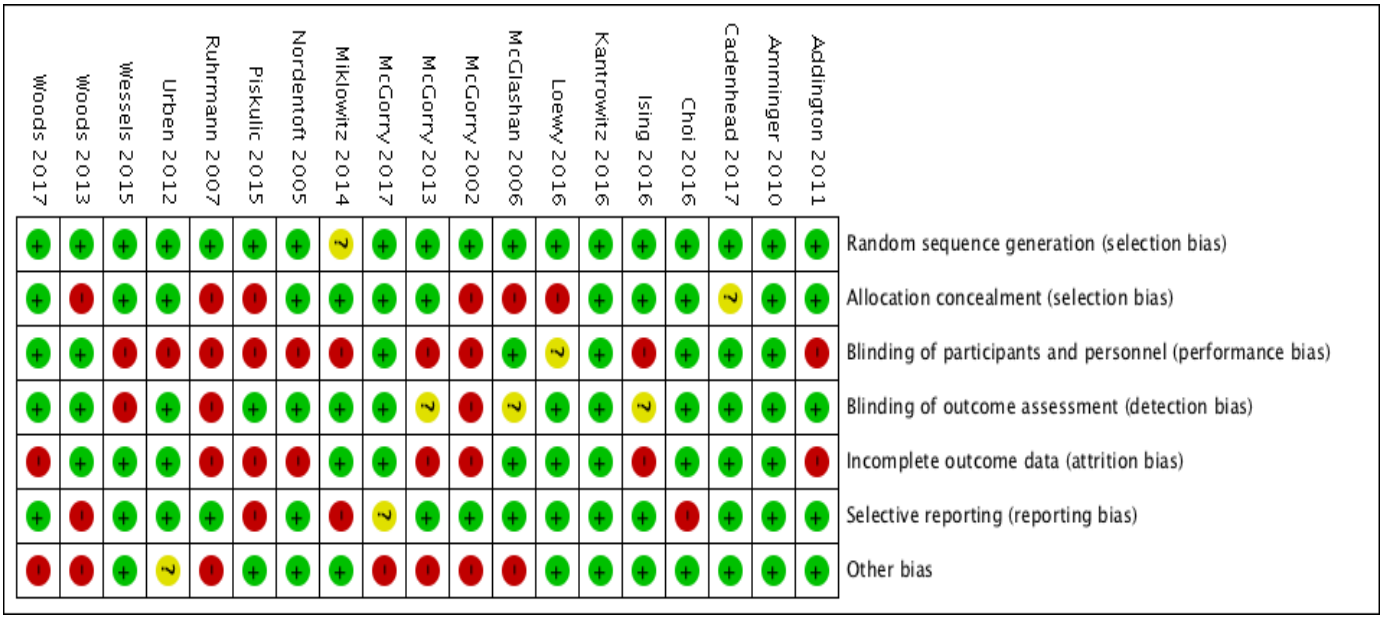
Quality assessment of RCTs (*N* = 19) is reported in Figure 2. Most RCTs had a low risk of bias for random sequence generation (*N* = 18) and selective reporting (*N* = 14). Studies had a high risk of bias for allocation concealment (*N* = 6), attrition bias (*N* = 8), and other bias due to funding (*N* = 7). Blinding of outcome assessment had an unclear risk of bias (*N* = 3) and a high risk of bias (*N* = 3). Blinding of participants and personnel had the highest risk of bias (*N* = 10). Risk of bias assessment in the NMA plot (figure 3) for blinding of outcome assessments demonstrated that 7 had a low risk of bias, 5 had an unclear risk of bias, and 3 had a high risk of bias. Quality assessment for GRADE and NOS are provided in Supplementary Material 4.

Figure 2.2 Risk of bias graph for RCTs

A.

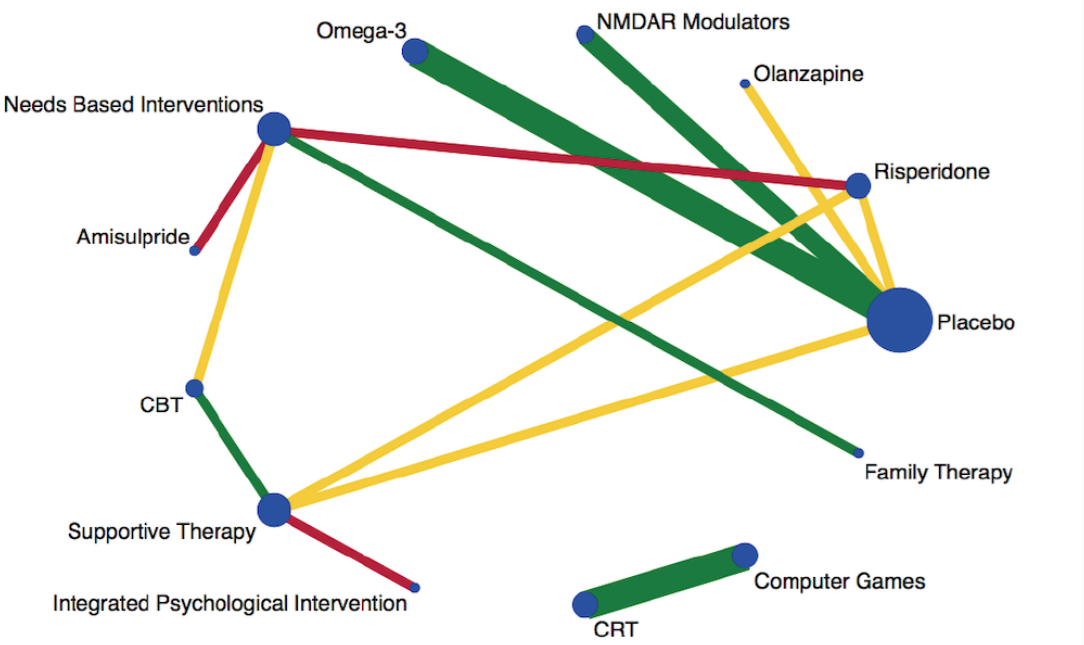


B.



A. Risk of bias graph for RCTs: review authors' judgements about each risk of bias item presented as percentages across all included studies.
B. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Figure 2.3 Negative Symptom Network Plot



Plot of the negative symptom network. Nodes are weighted according to the number of studies including the respective interventions. Edges are weighted according to the number of studies including either that treatment or that comparison. Colored edges (Green = Low Risk, Yellow = Unclear Risk, Red = High Risk) according to risk of bias for blinding of outcome assessments, estimated as the level of bias in the majority of the trials and weighted according to the number of studies in each comparison.

2.5.5 Publication Bias

Visual inspection of the network comparison-adjusted funnel plot for symmetry indicated the absence of small study effects, see Supplementary Material 5.

2.5.6 Transitivity

Transitivity can be measured by inconsistency between direct and several indirect effect estimates using triangular or quadratic loops (e.g., four treatments compared within the loop).[84] The inconsistency plot produced one quadratic loop which found no significant evidence of inconsistency between direct and indirect evidence in the NMA, see Supplementary Material 5.

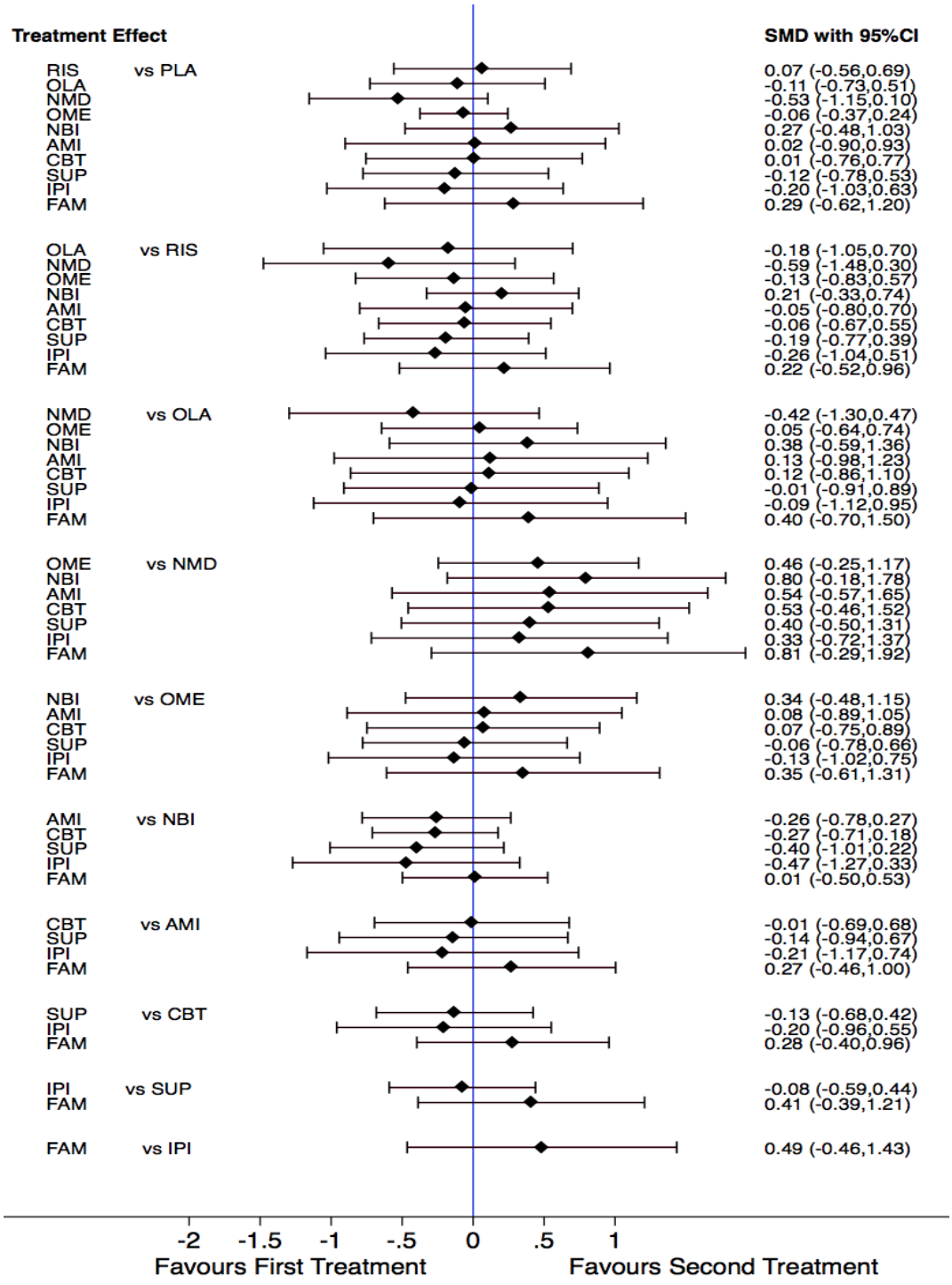
2.5.7 Primary and Secondary Outcomes

2.5.7.1 NMDAR Modulators

Three NMDAR modulator (glycine and D-serine) interventions reported on negative symptoms. Two NMDAR modulator (glycine and D-serine) interventions including 52 participants had sufficient data for meta-analysis (Supplementary Material 6). NMDAR modulator interventions were not associated with a significant reduction in negative symptoms compared to placebo (SMD, -0.54; 95% CI, -1.09 to 0.02; I^2 = 0%; P = 0.06, Supplementary Material 6). In the NMA NMDAR modulators consistently demonstrated small to large effect sizes for negative symptom reduction compared to the majority of interventions; risperidone (SMD −0.59; 95% CI, −1.48 to 0.30), olanzapine (SMD −0.42; 95% CI, −1.30 to 0.47), amisulpride (SMD 0.54; 95% CI, −0.57 to 1.65), CBT (SMD 0.53; 95% CI, −0.46 to 1.52), supportive therapy (SMD 0.40; 95% CI, −0.50 to 1.31), family therapy (SMD 0.81; 95% CI, −0.29 to 1.92), needs based interventions (SMD 0.80; 95% CI, −0.18 to 1.78), integrated psychological interventions

(SMD 0.33; 95% CI, −0.72 to 1.37), and omega-3 (SMD 0.46; 95% CI, −0.25 to 1.17), (figure 4). Lastly, SUCRA plots of the absolute effects and rank test indicated that NMDAR modulators were the most effective interventions for reducing total negative symptom scores compared to all other interventions (see Supplementary Material 5).

Figure 2.4 Network Forest Plot



2.5.7.2 Omega-3

Three omega-3 studies reported on negative symptoms at 6 and 12 months. Three studies including 375 participants had sufficient data for meta-analysis (Supplementary Material 6). Omega-3 interventions were not associated with a significant reduction in negative symptoms at 6 or 12-month follow-up compared to placebo (SMD, -0.26; 95% CI, -0.86 to 0.35; I_2 = 86%; P = 0.40 vs SMD, -0.06; 95% CI, -0.46 to 0.35; I_2 = 63%; P = 0.78). In the NMA omega-3 demonstrated small to medium effects sizes for negative symptom reduction compared to needs based interventions (SMD 0.34; 95% CI, −0.48 to 1.15) and family therapy (SMD 0.35; 95% CI, −0.61 to 1.31). Omega-3 had no effect compared to risperidone (SMD -0.13; 95% CI, −0.83 to 0.57), olanzapine (SMD 0.05; 95% CI, −0.64 to 0.74), amisulpride (SMD 0.08; 95% CI, −0.89 to 1.05), CBT (SMD 0.07; 95% CI, −0.75 to 0.89), supportive therapy (SMD -0.06; 95% CI, −0.78 to 0.66), and integrated psychological interventions (SMD -0.13; 95% CI, −1.02 to 0.75) (figure 4).

2.5.7.3 Psychosocial Interventions

Three CBT studies including 236 participants had sufficient data for meta-analysis (Supplementary Material 6). CBT interventions were not associated with a significant reduction in negative symptoms compared to controls (SMD, -0.12; 95% CI, -0.37 to 0.14; I_2 = 0%; P = 0.37, Supplementary Material 6). In the NMA CBT appears to be more effective at reducing negative symptoms than needs based interventions (SMD, -0.27; 95% CI, -0.71 to 0.18) and family therapy (SMD, 0.28; 95% CI, -0.40 to 0.96) (figure 4).

Three family therapy studies reported negative symptoms; only two studies including 211 participants had sufficient data for a paired pre/post meta-analysis (Supplementary Material 6). Family therapy was not associated with a significant reduction in negative symptoms but demonstrated a large effect size in the absence of a control (SMD, -1.17; 95% CI, -3.29 to 0.95; I_2 = 0%; P = 0.28, Supplementary Material 6). However, in the NMA family therapy did not appear to be more effective than any other treatment (figure 4).

Integrated psychological interventions could only be combined in the NMA due to having only one available study. Integrated psychological interventions appears to be more effective than needs based interventions (SMD, -0.47; 95% CI, -1.27 to 0.33), family therapy (SMD, 0.49; 95% CI, -0.46 to 1.43), CBT (SMD, -0.20; 95% CI, -0.96 to 0.55), amisulpride (SMD, -0.21; 95% CI, -1.17 to 0.74), and risperidone (SMD -0.26; 95% CI, −1.04 to 0.51). Needs based interventions did not appear to be more effective than any other treatment (figure 4). Lastly, supportive therapy appears to be more effective than needs based interventions (SMD, -0.40; 95% CI, -1.01 to 0.22) and family therapy (SMD, 0.49; 95% CI, -0.46 to 1.43) in the NMA.

2.5.7.4 Antipsychotics

Two risperidone studies (both included a CBT component) reported on negative symptoms at 6 and 12 months; both studies including 146 participants had sufficient data for meta-analysis (Supplementary Material 6). Risperidone interventions were not associated with a significant reduction in negative symptoms at 6 or 12-month follow-up (MD, 0.09; 95% CI, -7.63 to 7.81; I_2 = 64%; P = 0.98 vs MD, 0.41; 95% CI, -4.45 to 5.28; I_2 = 0%; P = 0.87, Supplementary Material 6). Risperidone in the NMA appears to be

more effective at reducing negative symptoms than needs based interventions (SMD, 0.21; 95% CI, -0.33 to 0.74) and family therapy (SMD, 0.22; 95% CI, -0.52 to 0.96) (figure 4).

Three aripiprazole studies reported on paired pre/post negative symptoms; all three studies including 61 participants had sufficient data for meta-analysis (Supplementary Material 6). Aripiprazole interventions were associated with a significant reduction in negative symptoms (SMD, -0.66; 95% CI, -1.03 to -0.30; I_2 = 0%; P < 0.01, Supplementary Material 6). Aripiprazole interventions could not be combined in the NMA due to having no comparable control.

Amisulpride and olanzapine could only be combined in the NMA due to having only one available study each. Amisulpride appears to be more effective at reducing negative symptoms than needs based interventions (SMD, -0.26; 95% CI, -0.78 to 0.27) and family therapy (SMD, 0.27; 95% CI, -0.46 to 1.00). Olanzapine appears to be more effective than needs based interventions (SMD, 0.38; 95% CI, -0.59 to 1.36) and family therapy (SMD, 0.40; 95% CI, -0.70 to 1.50) at reducing negative symptoms.

2.5.7.5 Cognitive remediation therapy

Six cognitive remediation therapy (CRT) studies reported on negative symptoms; only three studies including 154 participants had sufficient data for meta-analysis (Supplementary Material 6). CRT interventions were not associated with a significant reduction in negative symptoms compared to computer games (SMD, 0.21; 95% CI, -0.12 to 0.53; I_2 = 0%; P = 0.21, Supplementary Material 6). No CRT studies were assessed in the NMA due to having no comparable intervention, denoted by having no connecting node in the network plot (figure 3).

2.6.1 Discussion

We compared the effects of NMDAR modulators, omega-3, antipsychotics, psychosocial interventions, CRT, needs based interventions, and integrated psychological interventions in individuals at CHR for psychosis on negative symptoms using pairwise meta-analyses, paired pre/post meta-analyses, and a NMA. No treatments significantly reduced negative symptoms and in the NMA all confidence intervals overlapped the null line. NMDAR modulators were not significantly better than placebo but in the NMA emerged more effective than risperidone, olanzapine, omega-3, amisulpride, CBT, supportive therapy, family therapy, needs based interventions, integrated psychological interventions, and combination therapies at reducing negative symptoms in CHR youth. Omega-3 interventions were found to be better than family therapy and needs based interventions in the NMA, but the effect sizes were usually small and were not significant compared to placebo in pairwise meta-analysis. Antipsychotics fared better than needs based interventions and family therapy in the NMA. Aripiprazole produced a significant reduction in negative symptoms but in the absence of a control group. Psychosocial interventions (CBT, family therapy, supportive therapy) were not more efficacious than placebo in reducing negative symptoms in both pairwise meta-analyses and the NMA. Both Omega-3 and risperidone pairwise meta-analyses demonstrated significant amounts of heterogeneity however in meta-analyses of very few studies such as this the I^2 may not be accurate.[119]

Antipsychotics function primarily to block dopamine receptors, targeting positive symptoms, but seem to have little impact on negative symptoms in CHR youth compared to placebo.[54] However, amisulpride and olanzapine both showed favorable results at the reduction of negative symptoms compared to other interventions such as

needs based interventions and family therapy. An improvement in negative symptoms has been shown in amisulpride and olanzapine treatment with low-dose amisulpride (50-100 mg/day) and olanzapine in schizophrenia patients.[120,121] Finally, none of the needs based, CBT, and supportive therapy arms targeted negative symptoms in CHR and thus the results may be merely emphasizing the fact that these interventions were not designed to reduce negative symptoms.

NMDAR antagonists (phencyclidine and ketamine) can induce cognitive and behavioral changes comparable to patients with schizophrenia, thus formulating the NMDAR modulator postulate.[28-30] In addition to the results here for NMDAR modulators in CHR youth, there are mixed results in improving negative symptoms for those with schizophrenia.[31] Only three studies on NMDAR modulators in CHR youth exist to date, all of which have been pilot studies. Pilot studies represent a foundational step in investigating novel interventions such as NMDAR modulators. However, the NMDAR modulator pilot studies should be interpreted with caution as they require subsequent implementation in larger samples to determine a precise and meaningful effect size that is generalizable beyond the inclusion and exclusion criteria of the respective pilot design.[122] Moreover, NMDAR modulator studies to date suffer from small sample sizes and the results of the NMA should be interpreted with caution until larger trials investigating the impact of NMDAR modulator in CHR samples emerge. Lastly, glycine and d-serine are not equally encouraging for the reduction of negative symptoms in CHR, which was demonstrated in the results of the pairwise meta-analysis. Efficacy of NMDAR modulators has varied, with patients needing larger doses of glycine while d-serine is tolerated in much smaller doses.[97] Thus, *N*-acetylcysteine (NAC) may be an

important compound to investigate in CHR in regards to negative symptoms due to its effects on NMDAR functioning and having a mild side-effect profile.[123,124] Taking these limitations into account, NMDAR modulators taken in conjunction with psychosocial interventions and antipsychotics may prove to be an effective approach to treating the array of symptoms (e.g. positive, negative, disorganized) that CHR youth face, nevertheless larger trials are needed.

2.6.2 Strengths and limitations

This review included 32 interventions with more than 2,400 CHR youth. We used a broad and rigorous approach to identify interventions, extracted outcomes in duplicate, and used sound meta-epidemiological methodology. Thus, making this review the most comprehensive systematic review of negative symptom interventions in CHR to date. However, our study has several limitations. First, there is a relative paucity of high-quality literature on interventions in CHR on negative symptoms. Although the majority of studies identified were RCTs, a large amount of attrition occurred, which may have introduced important biases in the meta-analyses. However, most RCTs had relatively balanced dropouts across groups and handled incomplete data with an intention-to-treat analysis, which may have attenuated attrition bias. Thus, attrition appears to be inherent in CHR samples and not due to a lack of efficacy in the RCTs. In addition, almost half of the RCTs had either an unclear or high risk of bias for blinding of outcome assessments which has been shown to be associated with an inflated estimate of effects.[67]

Second, paired pre/post non-randomized controlled studies can only establish an association between an intervention and negative symptoms. Therefore, even though

aripiprazole non-randomized controlled studies showed a significant decrease in negative symptoms and family interventions demonstrated a large effect size, neither results establish causality and should be interpreted with extreme caution. These studies are plagued with methodical problems such as confounders, sampling biases, and effect modifiers and rated poorly in quality assessments.

Third, the primary outcome for the majority of interventions was conversion to a psychotic disorder, a concomitant of attenuated psychotic symptoms. Consequently, studies were designed to decrease conversion rates, while negative symptoms were primarily juxtaposed as a secondary outcome with a battery of other secondary outcomes (e.g. cognition). Indeed, the recent meta-analysis of 168 RCTs that examined treatment for negative symptoms in schizophrenia resonates with our results that almost no studies were designed to target negative symptoms, nor used the required design for efficacy. In addition, it was observed that the literature was inconsistent on persistent negative symptoms, which was a subject that was not addressed in CHR trials.[24] The NIMH-MATRICS consensus on negative symptoms and a more recent perspective on methodological issues in negative symptom trials contend that the design of future trials targeting negative symptoms should take into account a variety of methodical considerations including a co-primary measure of functional improvement, optimal duration, investigation into interventions and agents that could have broad spectrum implications for both positive and negative symptoms, and addressing the strengths and weaknesses of available instruments for measuring negative symptoms.[32,33] Albeit, neither of the abovementioned perspectives considered CHR participants in their consensus, thus any future consensus on negative symptoms should include

schizophrenia, first episode, and high-risk researchers. Furthermore, most of the psychosocial treatments did not target negative symptoms failing to include elements designed to diminish negative symptoms. Thus, it may very well be that CBT in CHR, without a negative symptom component, is not effective for negative symptom reduction.

Fourth, we pooled a variety of negative symptom scales using SMD which may have important implications when interpreting the current results. The majority of studies employed the SOPS scale for measuring negative symptoms in CHR which measures social anhedonia, avolition, decreased expression of emotion, decreased experience of emotions and self, decreased ideational richness, and a deterioration of role function. However, it does not measure two of the five core negative symptoms, alogia and restricted affect, which has been established by the NIMH consensus. Interestingly, a new scale, the Prodromal Interview of Negative Symptoms (PINS) has recently been developed as a result of the consensus conference recommendations.[125] To date, however, this scale has only reported preliminary data on psychometric properties although plans for further development are underway.[125]

Fifth, the current results cannot disambiguate between primary negative symptoms (pathophysiological schizophrenia mechanisms) and secondary negative symptoms (other mechanisms such as depression). CHR youth samples often have high comorbid rates of depression and anxiety, which has been shown to be correlated with negative symptoms such as anhedonia.[126] None of the current studies utilized methods to reduce the influence of secondary negative symptoms nor provided a distinction between the two, which may have confounded the relationship between

negative symptom improvement or lack of improvement and their respective interventions. To this point our analysis cannot amend analytically issues of pseudospecificity and the current studies have important limitations related to the underreporting of both the persistence of negative symptoms in CHR and transience of these symptoms.

Lastly, the effect of omega-3 on negative symptoms in both the pairwise and NMA was strongly influenced by one small study conducted in 2010,[57] which failed to be replicated in two subsequent studies.[100,114] Thus, although omega-3 demonstrated a small effect compared to family therapy this would primarily be due to the presence of the 2010 study the data. Moreover, all omega-3 confidence intervals overlapped the null line in the NMA and it was not significant when compared to placebo in both analyses. Thus, the results of omega-3 should be interpreted with caution.

2.6.4 Directions for future research

The findings of the current systematic review lead to two potential areas for future research. First, NMDAR modulators (D-serine and glycine) were shown to have a moderate effect on negative symptoms and merit further investigations into other NMDAR modulators such as D-alanine and sarcosine, which may be effective early intervention for negative symptoms.[127] In addition, NMDAR modulators have shown promising results in the reduction of positive symptoms in CHR and may represent a treatment for wider range of symptomatology than psychotherapies or antipsychotics.[128] However, larger studies are needed to assess NMDAR modulators effects on quality of life, long-term outcomes of negative symptoms, and transition to a psychotic disorder[54] as well as side effects and compliance issues.

Second, aripiprazole non-randomized controlled studies produced a moderate effect on negative symptoms in the absence of a control group. However, one study compared aripiprazole to short-term antipsychotics in sample of ten CHR individuals and found no significant difference between groups.[116] Due to the poor study designs and being significantly under powered, a large randomized control trial is needed to understand the overall effect of aripiprazole on negative symptoms compared to controls.

Lastly, due to the pluripotent nature of the CHR state, those at risk may never develop psychosis, albeit many still suffer from reduced quality of life and low functioning and require evidence-based treatments.[129]

2.6.5 Conclusions

In conclusion, although this review demonstrated small-large effect sizes between interventions and a reduction in negative symptoms, many relevant studies had small samples and the majority were not designed to target negative symptoms, thus reducing their clinical importance with respect to negative symptoms. Future research should be undertaken in the form of large clinical trials that target negative symptoms in CHR.

2.7 Supplementary Material

Supplementary Material 1. Prisma Checklists for Both Pairwise and NMA

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5-6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary material 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I_2) for each meta-analysis.	8-10

Section/topic	**#**	**Checklist item**	**Reported on page #**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11-12
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12-13
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	13-17
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13-17
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12-13

Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	18
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	17-18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	19-20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20-21
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	21-22

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	
ABSTRACT			***2***
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings.	

		Other: primary source of funding; systematic review registration number with registry name.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, *including mention of why a network meta-analysis has been conducted.*	***3-4***
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	***4***
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	***4***
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	***5-6, Table 1***
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	***6-8***
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	***5, Supplementary Material 2***
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	***5-6***
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	***6***
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	***7-9***
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence	***8-9***

		base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	***6-7***
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	***7***
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	***8-9***
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	***8-9***
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	***6-7***
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	***8-9***
RESULTS†			

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	***9-10, Figure 1***
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	***10, Figure 3***
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	***10, Figure 3***
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	***10***
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	***11***
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	***11-14***
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	***11-14, Figure 4***
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	***11, Supplementary 5***
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	***11, Figure 2, Supplementary 4***
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	***11***
DISCUSSION			

Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	***15-20***
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	***17-21***
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	***22***
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	***22***

PICOS = population, intervention, comparators, outcomes, study design.

Supplementary Material 2. Search Strategies

Database: Embase

1 exp psychotic disorders/ (253448)
2 deficit syndrome.ti,ab. (471)
3 exp schizophrenia/ (167961)
4 ((chronic$ or serious or persistent or severe$) adj (mental$ or psychological$) adj (disorder$ or ill$)).mp. (11400)
5 (delusion$ or hebephreni$ or psychosis or psychoses or psychotic$ or schizo$).mp. (279220)
6 or/1-5 (305720)
7 risk factors/ (427284)
8 symptom$.sh. or (prodrom$ or risk$).hw. (2614940)
9 (blips or brief limited intermittent psychotic symptom$ or ((attenuat$ or early or pre?monitory) adj2 (sign$ or symptom$)) or pre?delusion$ or pre?hallucin$ or pre?psychos$ or pre?psychotic$ or pre?schizo$ or (pre adj (delusion$ or hallucin$ or psychos$ or psychotic$ or schizo$)) or prodrom$ or sub?clinical$ or sub?threshold$ or at risk$ or ((high$ or incipient or increas$) adj3 risk$)).ti,ab,kw. (1088955)
10 or/8-9 (2925711)
11 (conversion$ or ((develop$ or progress$) adj2 (psychos$ or psychotic$ or schiz$)) or first episode$ or fullthreshold$ or full threshold$ or onset$ or progression or transition$ or transitory).ti,ab. (1559662)
12 10 and 11 (268386)
13 clinical high risk.ti,ab. (818)
14 ultra high risk.ti,ab. (1384)
15 basic symptoms.ti,ab. (461)
16 attenuated psychosis syndrome.ti,ab. (97)
17 ((at risk or ((high or increase$) adj2 risk) or blips or brief limited intermittent psychotic symptom$ or ((attenuat$ or early or premonitory) adj2 (sign$ or symptom$)) or prodrom$ or subclinical$ or sub$ clinical$ or subthreshold or sub$ threshold) and (psychos$ or psychotic$ or schiz$)).ti. or ((at risk or ((high or increase$) adj2 risk) or blips or brief limited intermittent psychotic symptom$ or ((attenuat$ or earlyor premonitory) adj2 (sign$ or symptom$)) or prodrom$ or subclinical$ or sub$ clinical$ or subthreshold or sub$ threshold) adj3 (psychos$ or psychotic$ or schiz$)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading] (7837)
18 or/13-17 (8641)
19 negative symptom$.ti,ab. (11896)
20 (expression adj2 emotion*).ti,ab. (3410)
21 ideational richness.ti,ab. (13)
22 (role functioning or occupational functioning or school functioning).ti,ab. (3678)
23 (experience adj2 (emotion or self)).ti,ab. (2043)
24 (social anhedonia or social withdrawal).ti,ab. (2220)
25 (avolition or motivation).ti,ab. (51729)
26 or/19-25 (73455)
27 6 and (or/7,12,18) and 26 (1997)

Database: Ovid MEDLINE(R)

1 exp psychotic disorders/ (50020)
2 deficit syndrome.ti,ab. (389)
3 exp schizophrenia/ (105295)
4 ((chronic$ or serious or persistent or severe$) adj (mental$ or psychological$) adj (disorder$ or ill$)).mp. (9904)
5 (delusion$ or hebephreni$ or psychosis or psychoses or psychotic$ or schizo$).mp. (224588)
6 or/1-5 (230778)
7 risk factors/ (726591)
8 symptom$.sh. or (prodrom$ or risk$).hw. (1051779)
9 (blips or brief limited intermittent psychotic symptom$ or ((attenuat$ or early or pre?monitory) adj2 (sign$ or symptom$)) or pre?delusion$ or pre?hallucin$ or pre?psychos$ or pre?psychotic$ or pre?schizo$ or (pre adj (delusion$ or hallucin$ or psychos$ or psychotic$ or schizo$)) or prodrom$ or sub?clinical$ or sub?threshold$ or at risk$ or ((high$ or incipient or increas$) adj3 risk$)).ti,ab,kw. (846231)
10 or/8-9 (1614662)
11 (conversion$ or ((develop$ or progress$) adj2 (psychos$ or psychotic$ or schiz$)) or first episode$ or fullthreshold$ or full threshold$ or onset$ or progression or transition$ or transitory).ti,ab. (1350820)
12 10 and 11 (134026)
13 clinical high risk.ti,ab. (599)
14 ultra high risk.ti,ab. (829)
15 basic symptoms.ti,ab. (266)
16 attenuated psychosis syndrome.ti,ab. (70)
17 ((at risk or ((high or increase$) adj2 risk) or blips or brief limited intermittent psychotic symptom$ or ((attenuat$ or early or premonitory) adj2 (sign$ or symptom$)) or prodrom$ or subclinical$ or sub$ clinical$ or subthreshold or sub$ threshold) and (psychos$ or psychotic$ or schiz$)).ti. or ((at risk or ((high or increase$) adj2 risk) or blips or brief limited intermittent psychotic symptom$ or ((attenuat$ or earlyor premonitory) adj2 (sign$ or symptom$)) or prodrom$ or subclinical$ or sub$ clinical$ or subthreshold or sub$ threshold) adj3 (psychos$ or psychotic$ or schiz$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (5939)
18 or/13-17 (6450)
19 negative symptom$.ti,ab. (9177)
20 (expression adj2 emotion*).ti,ab. (2900)
21 ideational richness.ti,ab. (8)
22 (role functioning or occupational functioning or school functioning).ti,ab. (2754)
23 (experience adj2 (emotion or self)).ti,ab. (1753)
24 (social anhedonia or social withdrawal).ti,ab. (1723)
25 (avolition or motivation).ti,ab. (51025)
26 or/19-25 (68304)
27 6 and (or/7,12,18) and 26 (1078)

Database: EBM Reviews - Database of Abstracts of Reviews of Effects

1 psychotic disorders.mp. (114)
2 deficit syndrome.mp. (0)
3 schizophrenia.mp. (402)
4 ((chronic* or serious or persistent or severe*) adj (mental* or psychological*) adj (disorder* or ill*)).mp. (70)
5 (delusion* or hebephreni* or psychosis or psychoses or psychotic* or schizo*).mp. (554)
6 1 or 2 or 3 or 4 or 5 (598)
7 risk factors.mp. (2761)
8 (symptom* or (prodrom* or risk*)).mp. (12470)
9 (blips or brief limited intermittent psychotic symptom* or ((attenuat* or early or pre?monitory) adj2 (sign* or symptom*)) or pre?delusion* or pre?hallucin* or pre?psychos* or pre?psychotic* or pre?schizo* or (pre adj (delusion* or hallucin* or psychos* or psychotic* or schizo*)) or prodrom* or sub?clinical* or sub?threshold* or at risk* or ((high* or incipient or increas*) adj3 risk*)).mp. (10903)
10 or/8-9 (12479)
11 (conversion* or ((develop* or progress*) adj2 (psychos* or psychotic* or schiz*)) or first episode* or fullthreshold* or full threshold* or onset* or progression or transition* or transitory).mp. (1768)
12 10 and 11 (1167)
13 clinical high risk.mp. (0)
14 ultra high risk.mp. (3)
15 basic symptoms.mp. (1)
16 attenuated psychosis syndrome.mp. (0)
17 ((at risk or ((high or increase*) adj2 risk) or blips or brief limited intermittent psychotic symptom* or ((attenuat* or early or premonitory) adj2 (sign* or symptom*)) or prodrom* or subclinical* or sub* clinical* or subthreshold or sub* threshold) and (psychos* or psychotic* or schiz*)).ti. or ((at risk or ((high or increase*) adj2 risk) or blips or brief limited intermittent psychotic symptom* or ((attenuat* or earlyor premonitory) adj2 (sign* or symptom*)) or prodrom* or subclinical* or sub* clinical* or subthreshold or sub* threshold) adj3 (psychos* or psychotic* or schiz*)).mp. (33)
18 or/13-17 (33)
19 negative symptom$.mp. (49)
20 (expression adj2 emotion*).mp. (4)
21 ideational richness.mp. (0)
22 (role functioning or occupational functioning or school functioning).mp. (14)
23 (experience adj2 (emotion or self)).mp. (3)
24 (social anhedonia or social withdrawal).mp. (3)
25 (avolition or motivation).mp. (159)
26 19 or 20 or 21 or 22 or 23 or 24 or 25 (231)
27 6 and (7 or 12 or 18) and 26 (12)

Database: PsycINFO

1 psychotic disorders.mp. (5853)
2 deficit syndrome.mp. (355)
3 schizophrenia.mp. (111857)
4 ((chronic* or serious or persistent or severe*) adj (mental* or psychological*) adj (disorder* or ill*)).mp. (13090)
5 (delusion* or hebephreni* or psychosis or psychoses or psychotic* or schizo*).mp. (172838)
6 1 or 2 or 3 or 4 or 5 (182163)
7 risk factors.mp. (87803)
8 (symptom* or (prodrom* or risk*)).mp. (568277)
9 (blips or brief limited intermittent psychotic symptom* or ((attenuat* or early or pre?monitory) adj2 (sign* or symptom*)) or pre?delusion* or pre?hallucin* or pre?psychos* or pre?psychotic* or pre?schizo* or (pre adj (delusion* or hallucin* or psychos* or psychotic* or schizo*)) or prodrom* or sub?clinical* or sub?threshold* or at risk* or ((high* or incipient or increas*) adj3 risk*)).mp. (148104)
10 or/8-9 (576916)
11 (conversion* or ((develop* or progress*) adj2 (psychos* or psychotic* or schiz*)) or first episode* or fullthreshold* or full threshold* or onset* or progression or transition* or transitory).mp. (204266)
12 10 and 11 (56108)
13 clinical high risk.mp. (391)
14 ultra high risk.mp. (623)
15 basic symptoms.mp. (331)
16 attenuated psychosis syndrome.mp. (71)
17 ((at risk or ((high or increase*) adj2 risk) or blips or brief limited intermittent psychotic symptom* or ((attenuat* or early or premonitory) adj2 (sign* or symptom*)) or prodrom* or subclinical* or sub* clinical* or subthreshold or sub* threshold) and (psychos* or psychotic* or schiz*)).ti. or ((at risk or ((high or increase*) adj2 risk) or blips or brief limited intermittent psychotic symptom* or ((attenuat* or earlyor premonitory) adj2 (sign* or symptom*)) or prodrom* or subclinical* or sub* clinical* or subthreshold or sub* threshold) adj3 (psychos* or psychotic* or schiz*)).mp. (4779)
18 or/13-17 (5135)
19 negative symptom$.mp. (11272)
20 (expression adj2 emotion*).mp. (6253)
21 ideational richness.mp. (5)
22 (role functioning or occupational functioning or school functioning).mp. (2905)
23 (experience adj2 (emotion or self)).mp. (3915)
24 (social anhedonia or social withdrawal).mp. (2417)
25 (avolition or motivation).mp. (105269)
26 19 or 20 or 21 or 22 or 23 or 24 or 25 (130279)
27 6 and (7 or 12 or 18) and 26 (3112)

Database: CINHAL Plus

S1 MH "Psychotic Disorders+") OR "psychotic disorders" OR (MH "Schizophrenia+") OR "schizophrenia" (89,347)

S2 "ultra high risk" OR "clinical high risk" OR "basic symptoms" OR "attenuated psychosis syndrome" or "conversion" OR "transition" or (MH "Risk Factors") OR "risk factors" (305,483)

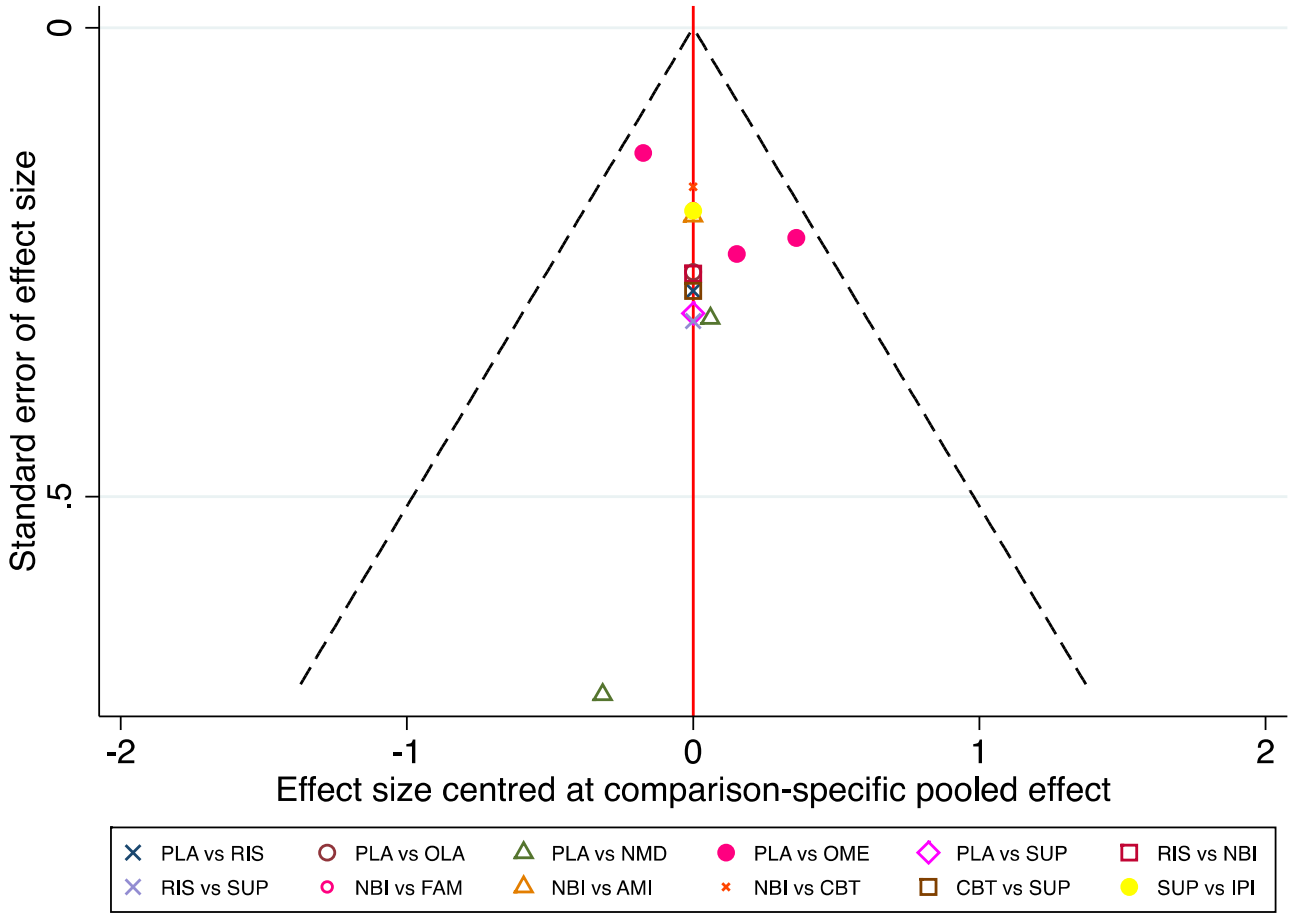
S3 "negative symptoms" OR "expression of emotion" OR "ideational richness" OR "role functioning" OR "school functioning" OR "occupational functioning" OR "experience of emotion" OR (MH "Anhedonia") OR "anhedonia" OR (MH "Motivation") OR "motivation" OR "avolition" (34,163)

S4 S1 AND S2 AND S3 (181)

Supplementary Material 3. Description of the Network Meta-Analysis with References

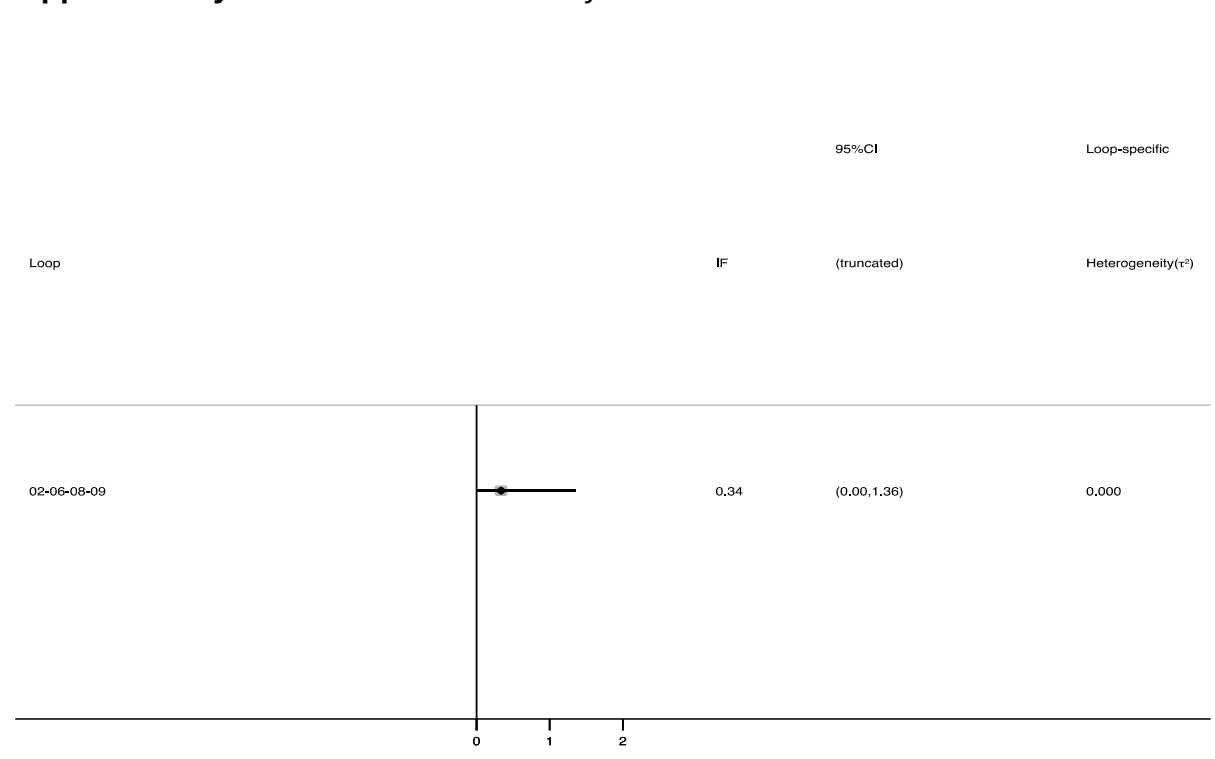
As stated, the NMA allowed for comparisons between treatment arms that have not been compared before (e.g. omega-3 to glycine to antipsychotics, etc.) that used a common comparator (e.g. placebo) by integrating direct evidence (e.g. 3 studies comparing omega-3 to placebo).[79] Only RCTs treatment effects between individual RCT intervention arms were evaluated using a random-effects multivariate NMA assuming consistency and a common heterogeneity across all comparisons in the network model using the generic inverse-variance method.[77,78] Any study that was observational or any arm in a RCT that was observational in nature was excluded from the NMA. Moreover, any study including participants other than CHR were excluded from the NMA (e.g., schizotypy). In addition, data in the NMA used follow-up scores adjusting the mean of the follow-up scores using regression as described in Dias et al., 2012.[1] Next, the formulae for Hedges' *g* detailed by White and Thomas (2005)[130] was used to calculate the SMD for the NMA, which is considered an unbiased estimator and involves corrections for small numbers of degrees of freedom. Due to the differences in treatment types (i.e. antipsychotics, nutritional supplements, psychotherapy) and differences in dose the primary duration reported in the NMA was the primary outcome endpoint reported in the RCTs. We opted for a random effects Multivariate Network Meta-Analysis as described by White et al 2013 [131] and Higgins 2013[132] because it can handle multiple treatment arms (more than 2 arms in one RCT)[133] which was expected in CHR RCTs and properly accounts for correlations between effect sizes from multi-arm RCTs.[133]

Supplementary Material 5. Network comparison-adjusted funnel plot



Comparison-adjusted funnel plot for the negative symptom network. Zero represents the null hypothesis that the study-specific effect sizes do not differ from the respective comparison-specific pooled effect estimates. Different colours correspond to different comparisons. Abbreviations: PLA = Placebo; RIS = Risperidone; OLA = Olanzapine; NMD = N-methyl-D-aspartate Receptor Modulators; OME = Omega-3; NBI = Needs Based Interventions; AMI = Amisulpride; CBT = Cognitive Behavioral Therapy; SUP= Supportive-Therapy; IPI = Integrated Psychological Interventions; FAM = Family-Therapy

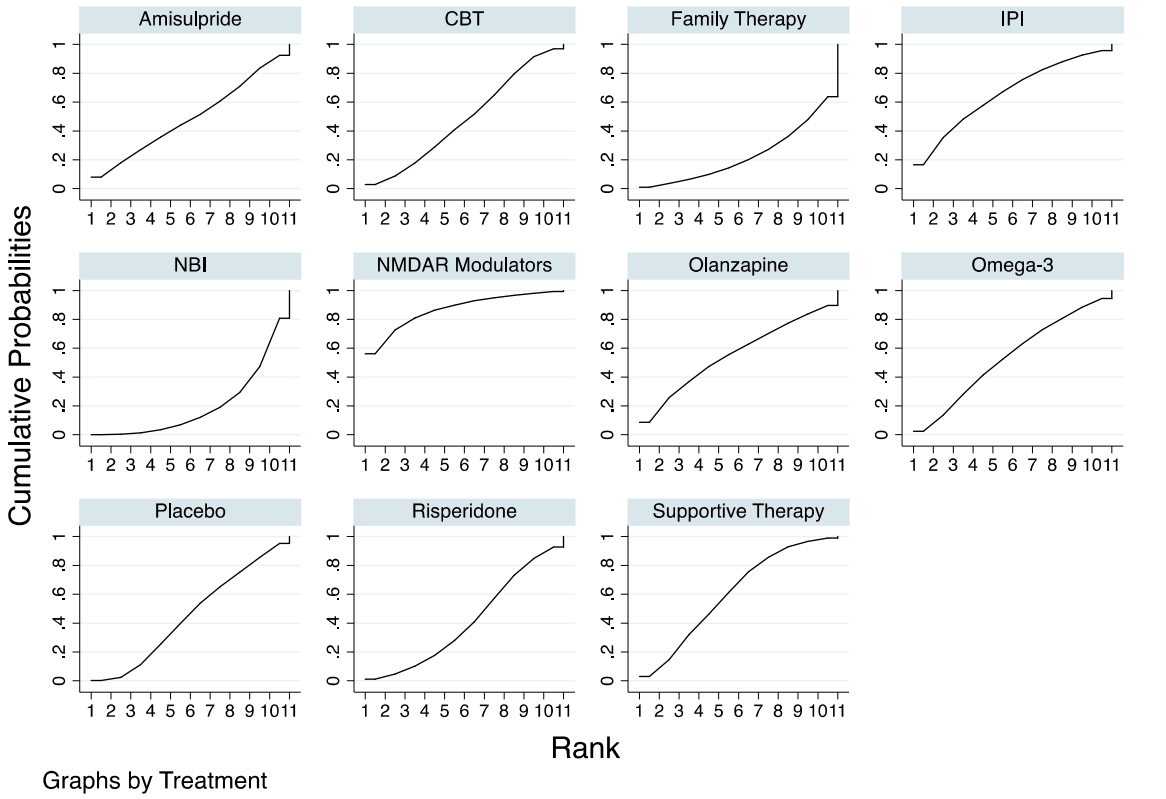
Supplementary Material 5. Inconsistency Plot



Loop	IF	seIF	z_value	p_value	CI_95	Loop_Heterog_tau2
02-06-08-09	0.336	0.524	0.641	0.521	(0.00,1.36)	0.000

Inconsistency plot produced one quadratic loop. Abbreviations: 02 = Risperidone; 06 = Needs Based Interventions; 08=Cognitive Behavioral Therapy; 09 = Supportive

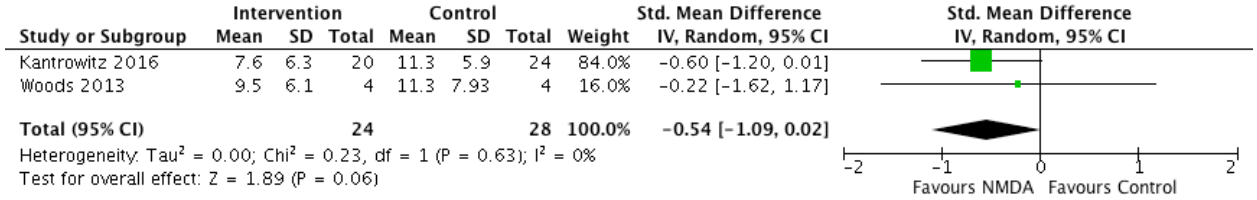
Supplementary Material 5. Surface under the cumulative ranking curve (SUCRA)



Plots of the surface under the cumulative ranking curves for all treatments in the negative symptom network. Black solid lines correspond to the unadjusted model. Abbreviations: NBI = Needs Based Interventions; CBT = Cognitive Behavioral Therapy; IPI = Integrated Psychological Interventions

Supplementary Material 6. Pairwise Forest Plots

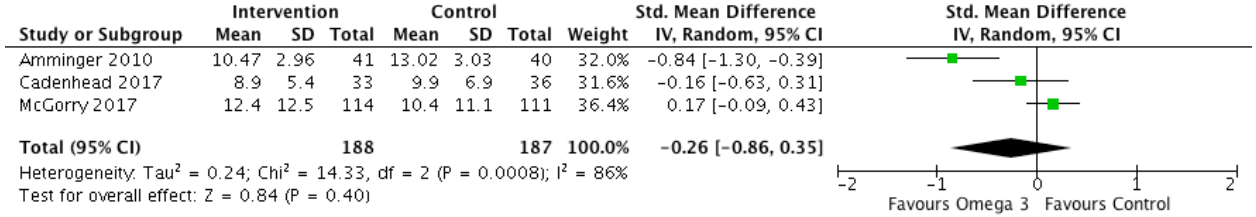
1) **NMDAR**



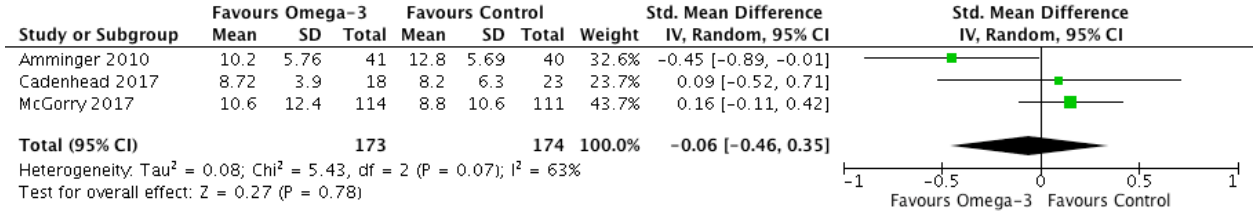
NMDAR impact on negative symptom scores in CHR.

2) **Omega-3**

A.



B.

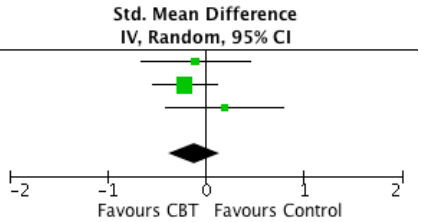


Omega 3 impact on negative symptom scores in CHR at (A) 6 months and (B) 12 months.

3) **CBT**

Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Addington 2011	4.4	4.3	27	4.9	5.3	24	21.8%	-0.10 [-0.65, 0.45]
Ising 2016	2.8	2.8	71	3.5	3.6	69	59.7%	-0.22 [-0.55, 0.12]
McGorry 2013z	16.3	11.6	27	13.9	13.9	18	18.5%	0.19 [-0.41, 0.79]
Total (95% CI)			**125**			**111**	**100.0%**	**-0.12 [-0.37, 0.14]**

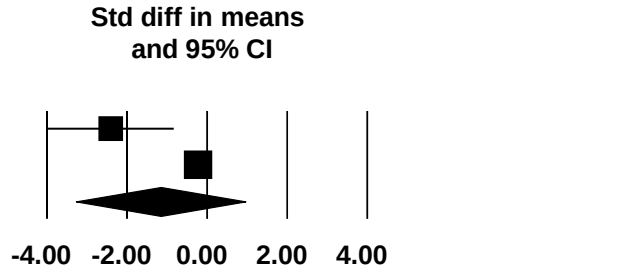
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.34$, df = 2 (P = 0.51); $I^2 = 0\%$
Test for overall effect: Z = 0.89 (P = 0.37)



CBT impact on negative symptom scores in CHR. z = CBT + Placebo vs Supportive + Placebo

4) **Family therapy**

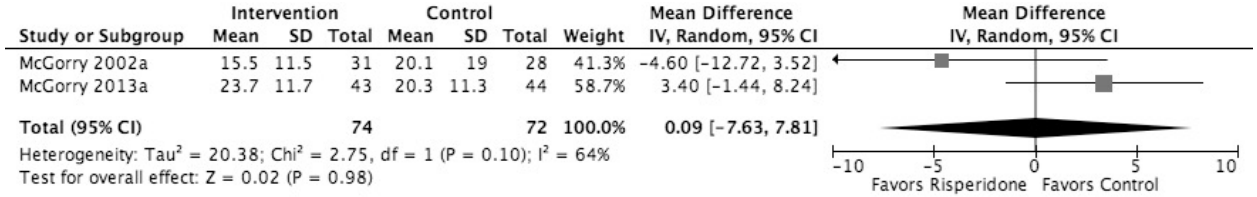
Study name	Std diff in means	Standard error	Lower limit	Upper limit
Landa 2015	-2.406	0.806	-3.985	-0.827
McFarlane 2015	-0.226	0.087	-0.397	-0.054
	-1.169	1.080	-3.286	0.948



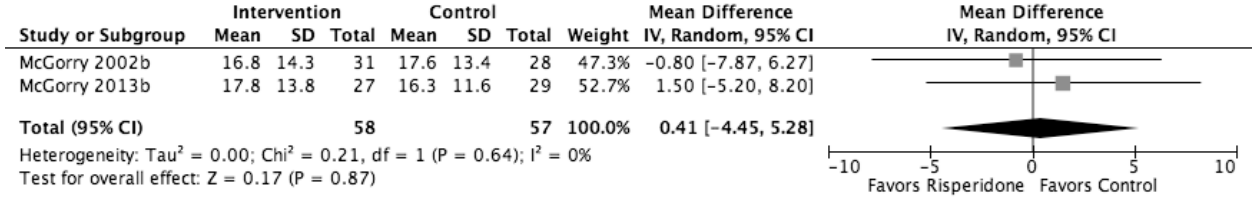
Family therapy observational interventions examining pre/post negative symptom scores in CHR, using only studies that used no CHR control group. Random effects model (Z= -1.082, P=0.279).

5) **Risperidone + CBT**

A.

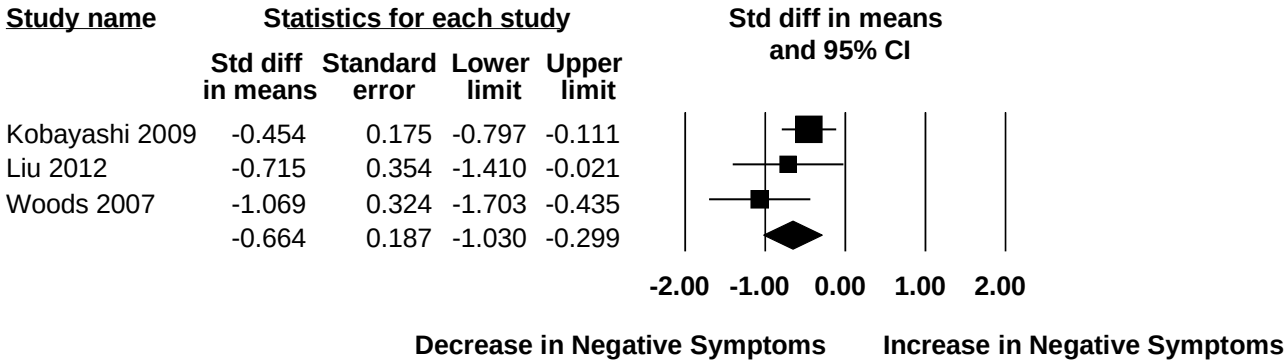


B.



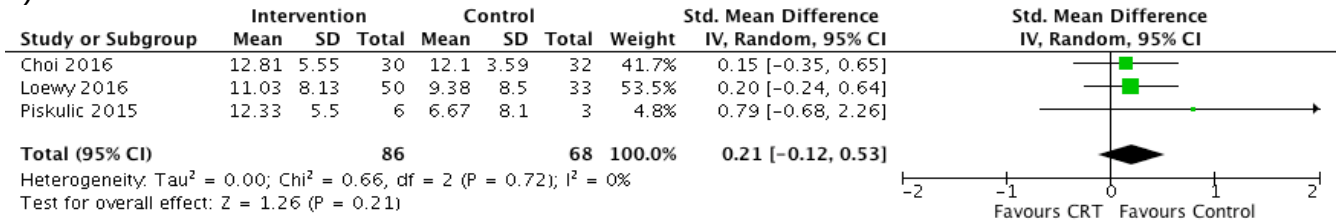
Risperidone + CBT vs Controls impact on negative symptom scores in CHR at (A) 6 months and (B) 12 months.

6) **Aripiprazole**



Aripiprazole observational interventions examining pre/post negative symptom scores in CHR. Random effects model (Z= -3.561, P=0.00).

7) **CRT**



CRT impact on negative symptom scores

Supplementary Material 4. Newcastle-Ottawa Scale Risk of Bias Assessment and GRADE

- **Newcastle-Ottawa Scale Risk of Bias Assessment**

Study Name	Study Type	Representativeness of the exposed cohort (A,B)*	Selection of the non exposed cohort (A)*	Ascertainment of exposure (A,B)*	Demonstration that outcome of interest was not present at start of study (A)*	Comparability of cohorts on basis of the design or analysis (A,B)*	Assessment of outcome (A,B)*	Was follow-up long enough for outcomes to occur (A)*	Adequacy of follow up of cohorts (A,B)*	Conclusions
Berger et al., 2008	Cohort	D - No description	C - No description	D - No description	B - Not stated (abstract only)	A - One group received low-dose lithium, with another UHR group only receiving supportive therapy	D - No description	NR - No description	D - Dropouts not reported	*
Cannon et al., 2002	Cohort	D - No statement as to where participants were taken from	C - Not controlled	C - Symptoms rated using average of self and parent reported ratings	A - Change score presented	NR - No controls	C - Self reports used to assess outcome	B - 12 week follow-up	B - Of the 6 patients who dropped out, one did because of adverse events	**
Fusar-Poli et al., 2015	Cohort	A - All participants refered to OASIS clinic in South London, from local area	D - All groups received CBT	B - Psychiatrist or clinical psychologist administers CAARMS	A - Change score presented	NR - All participants received CBT	D - Non-blinded interview	A - 6 years	B - 38 % dropped out (reasons described)	*** **
Hooker et al., 2014	Cohort	D - No statement as to where participants were taken from	A - Healthy controls group-matched CHR participants on IQ and demographics	B - Rated using structured interview for prodromal syndromes (SIPS)	A - Change score presented	A - Healthy controls recruited to preform computer-game control condition	B - Brain preformance index (BPI) used as standardized measure of Lumosity game preformance	B - No description	D - Dropouts not reported	*** **

Study Name	Study Type	Representativeness of the exposed cohort (A,B)*	Selection of the non exposed cohort (A)*	Ascertainment of exposure (A,B)*	Demonstration that outcome of interest was not present at start of study (A)*	Comparability of cohorts on basis of the design or analysis (A,B)*	Assessment of outcome (A,B)*	Was follow-up long enough for outcomes to occur (A)*	Adequacy of follow up of cohorts (A,B)*	Conclusions
Kobayashi et al., 2009	Cohort	B - Participants help-seeking outpatients from local metropolitan area	C - Uncontrolled study	B - SIPS performed on all patients with at-risk mental state	A - Change score presented	NR - No controls	D - Non-blinded interview	B - 12 week follow-up	B - 16.67% dropped out	*** *
Landa et al., 2016	Cohort	A - Participants recruited from New York City outpatient clinics and through advertisments	C - Open uncontrolled trial design	B - Assessments conducted by independent evaluator	A - Change score presented	NR - No controls	D - Only half blinded	B - 3 month follow up	A - No dropouts	*** *
Liu et al., 2012	Cohort	B - Recruited at study hospital	A - FEP and UHR participants recruited from hospital	B - Assessed using the PANSS	A - Change score presented	A - UHR vs FEP	D - Non-blinded interview	B - 28 days	B - 15.6% dropped out	*** ***
McFarlane et al., 2015	Cohort	D - 6 sites were used in the conduction of this study	A - All participants recommended for orientation before allocation	B - Independent research interviewers conducted all baseline and outcome assessments	A - Change score presented	A - Clinically low risk vs clinically high risk and first episode psychosis	A - Raters blinded to group assessment	A - 24 month	B - 34% dropped out after 2 years	*** *** *
Rauchensteiner et al., 2009	Cohort	B - Participants recruited from Early Recognition and Intervention Center (ERIC)	A - Both groups taken from ERIC	B - Assessed using the PANSS	A - Change score presented	A - Prodromal group vs schizophrena group	D - No description	B - No description	D - Dropouts not reported	*** **

Study Name	Study Type	Representativeness of the exposed cohort (A,B)*	Selection of the non exposed cohort (A)*	Ascertainment of exposure (A,B)*	Demonstration that outcome of interest was not present at start of study (A)*	Comparability of cohorts on basis of the design or analysis (A,B)*	Assessment of outcome (A,B)*	Was follow-up long enough for outcomes to occur (A)*	Adequacy of follow up of cohorts (A,B)*	Conclusions
Tsujino et al. 2013	Cohort	B - Help seeking outpatients	C - Uncontrolled study	B - Rated using structured interview for prodromal syndromes (SIPS)	A - Change score presented	NR - No controls	D - Non-blinded interview	B - 26 weeks	B - 27% dropped out	*** **
Washida et al., 2013	Cohort	A - Inpatients and outpatients who visited Zikei Hospital	A - All participants taken from Zikei Hospital	B - UHR group diagnopsed with CAARMS, FES/MEP group diagnosed with International classification of diseases	A - Change score presented	A - UHR vs FEP vs MEP	D - Non-blinded interview	B - 12 weeks	D - Dropouts not reported	*** ***
Woods et al., 2013	Cohort	A - Potential subjects informed about symptoms and risk of schizophrenia and invited to call research clinic if concerned.	C - Does not mention how control group was selected	B - Criteria of Psychosis-risk Syndromes (COPS) used to identify elegibility	A - Change score presented	A - Placebo controlled pilot study	D - Open-label trial	B - 12 weeks	B - 30% dropped out open-label glycine group, 15% dropped double-blind	*** **
Woods et al., 2007	Cohort	B - Participants were treatment-seeking out-patients	C - Uncontrolled study	B - SOPS used as primary efficacy measure	A - Change score presented	NR - No controls	D - Non-blinded interview	A - 52 weeks	B - 13% dropped out	*** **

GRADE

Intervention	Comparator	Study Name if Single Trial	Number of trials for direct comparison	Publication	Imprecision	Inconsistency	Indirectness	Study Limitations	Overall Quality (high, moderate, low, very low)
Omega-3	Placebo	N/A	3	Moderate - Comprehensive serach (no grey), no language restriction, industry influence	Low - Large sample size, outcome common, no serious adverse events	High - confidence not reported in all papers, heterogeneity apparent	Low	Low	Moderate
Risperidone	Needs Based Interventions	N/A	2	Moderate - Comprehensive serach (no grey), no language restriction, industry influence	Low - Adequate sample size, slight adverse events, similar outcome	Moderate- Not all papers reported confidence intervals, heterogeneity apparent	Moderate	High	Moderate
Nmdar Modulator	Placebo	N/A	2	Moderate - Comprehensive serach (no grey), no language restriction, industry influence	Moderate - Sample size relatively small, outcomes varied, No serious adverse events	High - No confidence interval reported, similar results and no p values reported	Moderate	Very Low	Moderate
Cognitive Behavioural Therapy	Supportive Therapy	Addington 2011	1	Low - Comprehensive serach (no grey), no language restriction, no industry influence	Moderate due to large confidence intervals	High - Substantial overlap of CIs	Low	Very Low	Moderate

Intervention	Comparator	Study Name if Single Trial	Number of trials for direct comparison	Publication	Imprecision	Inconsistency	Indirectness	Study Limitations	Overall Quality (high, moderate, low, very low)
Cognitive Behavioural Therapy	Needs Based Interventions	Ising 2016	1	Low - Comprehensive serach (no grey), no language restriction, no industry influence	Moderate due to large confidence intervals	High - Substantial overlap of CIs	Low	Low	Moderate
Olanzapine	Placebo	McGlashan 2006	1	Moderate - Comprehensive serach (no grey), no language restriction, industry influence	Moderate due to large confidence intervals	High - Substantial overlap of CIs	Low	High	High (industry and impercision)
Family-Focused Therapy	Needs Based Interventions	Miklowitz 2014	1	Low - Comprehensive serach (no grey), no language restriction, no industry influence	Moderate due to large confidence intervals	High - Substantial overlap of CIs	Low	Very Low	Moderate
Amisulpride	Needs Based Interventions	Ruhermann 2007	1	Low - Comprehensive serach (no grey), no language restriction, no industry influence	Moderate due to large confidence intervals	High - Substantial overlap of CIs	Low	Very Low	Moderate
Integrated Psychological Intervention	Supportive Therapy	Wessels 2015	1	Low - Comprehensive serach (no grey), no language restriction, no industry influence	Moderate due to large confidence intervals	High - Substantial overlap of CIs	Low	High	Moderate

Chapter 3: Persistent Negative Symptoms in Youth at Clinical High Risk for Psychosis: A Longitudinal Study

3.1 Preface

Research presented as part of this chapter has been published as; Daniel Devoe; Lu Lui; T.D. Cannon; K.S. Cadenhead; B.A. Cornblatt; T.H. McGlashan; D.O. Perkins; L.J. Seidman; M.T. Tsuang; S.W. Woods; E.F. Walker; D.H. Mathalon; C.E. Bearden; Jean Addington (2020). *Persistent Negative Symptoms in Youth at Clinical High Risk for Psychosis: A Longitudinal Study.* Schizophrenia Research.

Author Contributions: Drs. Addington, Cannon, Cadenhead, Cornblatt, McGlashan, Perkins, Seidman, Tsuang, Woods, Walker, Mathalon, and Bearden were responsible for the design of the study and for the supervisions of all aspects of data collection. Mr. Devoe and Ms. Liu were responsible for the statistical analyses. Mr. Devoe wrote the initial manuscript. Dr. Addington was involved in writing the subsequent drafts of the manuscript. All authors listed were involved in the study design and have contributed to and approved the final manuscript.

The only alterations made to this publication were for thesis formatting.

3.2 Abstract

Background: Severity of negative symptoms has been associated with poor functioning, cognitive deficits, and defeatist beliefs in schizophrenia patients. However, one area that remains understudied is persistent negative symptoms (PNS). Negative symptoms, including PNS, have been observed in those at clinical high-risk (CHR) for psychosis. The aim of this study was to determine if PNS were associated with functioning, neurocognition, and defeatist beliefs in a CHR sample.

Method: CHR participants (n=764) were recruited for the North American ProdromeLongitudinal Study. Negative symptoms were rated on the Scale of Psychosis-risk Symptoms. Generalized linear mixed models for repeated measures were used to examine changes over time between and within groups (PNS vs non-PNS).

Results: The PNS group (n=67) had significant deficits in functioning at baseline, 6, 12, 18, and 24-months compared to the non-PNS group (n=673). Functioning improved over time in the non-PNS group, while functioning in the PNS group remained relatively stable and poor over a two-year period. A consistent trend emerged demonstrating higher defeatist beliefs in the PNS group; however, this result was lost when controlling for persistent depressive symptoms. There were no significant differences between the groups on neurocognition, social cognition, and transition to psychosis.

Conclusions: PNS exist in youth at CHR for psychosis, resulting in significant and persistent functional impairment, which remains when controlling for persistent depressive symptoms. PNS remain even in CHR youth who do not transition to

psychosis. Thus, PNS may represent an unmet therapeutic need in CHR populations for which there are currently no effective treatments.

3.3 Introduction

Negative symptoms are a considerable cause of burden for schizophrenia patients, impacting both functioning and quality of life [134,135]. Although research has advanced our understanding of negative symptoms [134], one area that has remained relatively understudied is persistent negative symptoms (PNS, [135,136]. PNS are defined as clinically stable negative symptoms of moderate severity evident for an extended period of time, whilst controlling for potential sources of secondary negative symptoms (e.g., positive symptoms, extrapyramidal symptoms, or depression [136]. Although PNS research is limited, it is very clear from existing research that patients with PNS exhibit increased functional deficits [137-142], poorer quality of life [143], greater cognitive deficits [137], and have a longer prodrome [143] compared to schizophrenia patients without PNS. Fittingly, the NIMH-MATRICS [National Institute of Mental Health Measurement and Treatment Research to Improve Cognition in Schizophrenia] negative symptom consensus statement, identified PNS as an unmet therapeutic need in schizophrenia, for which longitudinal studies were identified as being invaluable [135]. The relationship between negative symptoms and functional deficits in patients with schizophrenia has been well documented [134,135], with deficits in functioning present long before the onset of illness [144,145]. One potential mechanism that has been proposed for negative symptoms and functional deficits are maladaptive cognitions such as defeatist performance beliefs [146,147]. The Beck model reasons that cognitions such as defeatist performance beliefs contribute to overall negative symptoms (e.g., amotivation and asociality) and functional deficits in schizophrenia [148,149]. Several observational studies support this model and have found a relationship between negative beliefs and negative symptoms [147-151]. A

recent meta-analysis in schizophrenia studies (k=10) found a significant effect between defeatist performance beliefs and both negative symptoms and functional outcomes [152]. Furthermore, research examining pathways contributing to functional deficits in schizophrenia has suggested a relationship between functional capacity, defeatist beliefs, and negative symptoms [153] with cognition having a direct effect on negative symptoms, and the combination of both cognition and negative symptoms having a direct effect on functional outcomes [154].

Furthermore, negative symptoms have been observed in those at clinical high risk (CHR) for psychosis [155,156]. Negative symptoms in those at CHR have associations with a wide range of symptoms and deficits such as social difficulties [157], depressive symptoms [158], cognitive deficits [159], and functional deficits [160]. However, CHR youth with PNS has rarely been investigated, with only one study to date examining the relationship between functioning and cognition in those with PNS. Moreover, those with predominant negative symptoms are not necessarily perceived as needing treatment [161]. In fact, no treatments to date have specifically targeted PNS in this population [162], thus an in-depth understanding of PNS in CHR is warranted.

CHR youth frequently exhibit functional deficits, doing poorly in school and work, and having increased social isolation [145], both of which have been shown to contribute to the likelihood of developing psychosis [145,160,163]. Deficits in social functioning appear to remain stable and unrelated to attenuated psychotic symptoms (APS).[145] However, many studies have demonstrated a relationship between negative symptoms and functional deficits in CHR [126,164-167], with long-standing negative symptoms associated with social difficulties [157].

A small study demonstrated that CHR youth endorsed defeatist beliefs more than healthy controls, and that these beliefs were associated with more severe negative symptoms [168]. Since defeatist performance beliefs are linked with increased severity of negative symptoms in schizophrenia [152] it may be important to investigate these beliefs in CHR youth who present with PNS. Indeed, previous studies identified CHR populations in particular as promising for improving our understanding of this relationship [152,168]

A recent meta-analysis demonstrated that CHR youth have poorer cognitive functioning than healthy controls, with the exception of social cognition [169]. Negative symptoms in CHR youth have been associated with poorer performance on verbal tasks and slower processing speed [156,170], with poorer performance on neurocognitive tests strongly associated with negative symptom severity [167]. Furthermore, one study demonstrated that poorer neurocognition was associated with more severe negative symptoms, while APS were not [171]. In terms of social cognition, one study demonstrated that facial affect processing and negative symptoms combined was the best model for predicting transition to psychosis [172], while other studies have not shown a relationship between social cognition and negative symptoms [173,174].

To date, several studies have demonstrated that negative symptoms typically occur prior to transition to psychosis [145,155,175-180]. With CHR individuals experiencing more severe negative symptoms at baseline having an increased risk of transition to psychosis [178] and in some cases negative symptoms have had a higher predictive value than APS [175,181]. Two studies have looked at the relationship between transition and PNS in CHR participants [155]. One study found no significant associations between PNS

and transition to psychosis (Yung et al., 2018). However, the study had few CHR participants with PNS (n=22) and employed the Buchanan PNS criteria [136], developed for schizophrenia and first-episode patients in clinical trials, which examines PNS over 6-months. The second study (n=138) demonstrated that negative symptoms were more severe and persistent in those who transitioned to psychosis [155]. Furthermore, this study showed that although severity of baseline negative symptoms predicted transition to psychosis, having PNS over 12-months was more predictive of transition.

Thus, identification and exploration of PNS in a large CHR longitudinal cohort may provide greater insight into when PNS first emerge. Determining whether PNS in CHR youth is directly related to functional deficits, cognitive deficits, defeatist beliefs, and transition may have important treatment implications, which may in turn impact long-term quality of life.

The present study examined PNS in CHR youth in a large longitudinal cohort [North American Prodrome Longitudinal Study (NAPLS 2)] [182] The aim of this current study was to: (1) determine the prevalence of PNS in a CHR sample, (2) define the relationship between PNS and functioning, defeatist beliefs, neurocognition and social cognition, and (3) to examine whether having PNS was associated with an increased risk of transition to psychosis. We hypothesized that CHR youth with PNS would show significant deficits in functioning, neurocognition, and present with more defeatist beliefs compared to CHR participants without PNS. In addition, we hypothesized that social cognition would not differ between the two groups. Furthermore, it was hypothesized that those with PNS would have an increased risk of transition to psychosis.

3.4 Methods

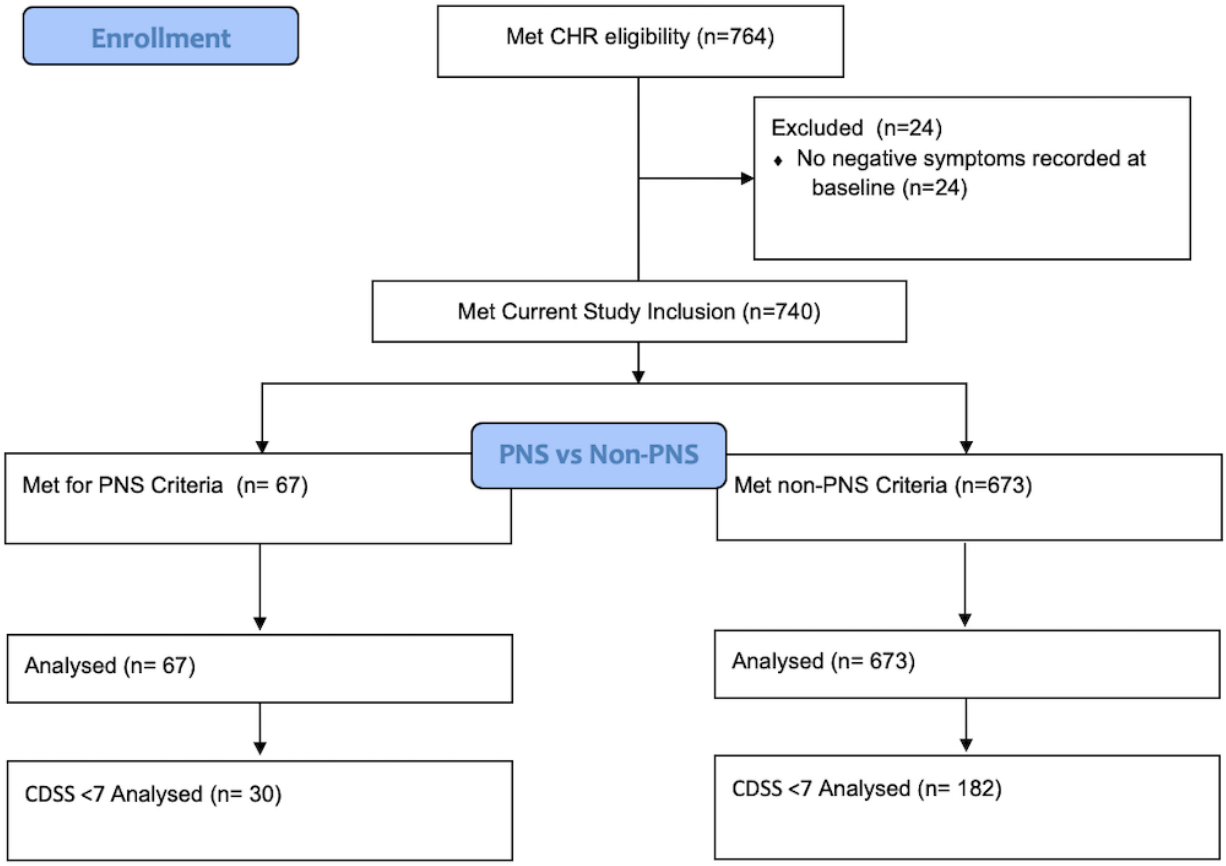
3.4.1 Setting and participants

All CHR participants (N=764; 436 males, 328 females) were recruited as part of the 8-site North American Prodrome Longitudinal Study [(NAPLS-2); University of California Los Angeles, Emory University, Harvard University, Zucker-Hillside Hospital, University of North Carolina, University of California San Diego, University of Calgary, and Yale University]. CHR participants between the ages of 12 and 35 years old were referred to NAPLS-2 by health care providers, social service agencies, educators, or were self-referred in response to community education efforts. Potential participants underwent a telephone screen to rule out any individuals who may already be psychotic and those for whom it seemed likely that they could meet COPS criteria were subsequently invited to an in-person eligibility evaluation and consent. At baseline, 743 participants met CHR criteria using the Criteria of Psychosis-risk Syndromes (COPS) based on the Structured Interview for Psychosis-risk Syndromes (SIPS) [36]. Twenty-one participants were considered high risk if they were under the age of 19 and presented with schizotypy. Exclusion criteria were any axis I current or lifetime psychotic disorder, IQ <70, past or current history of a central nervous system disorder, and substance dependence in the 6-months prior to enrollment. A more detailed description of the inclusion and exclusion criteria and study measures are described elsewhere [182,183].

For this study to determine the presence of PNS we included CHR participants who had negative symptoms scoring ≥4 at all 3 assessments: baseline, 6-months, and 12-months. Twenty-four participants did not have sufficient negative symptom data at baseline, leaving a sample of seven hundred and forty CHR participants. We included

all CHR subjects with negative symptoms who met criteria for PNS (*n*=67), as defined below, or who did not meet criteria; non-PNS (*n*=673), see Figure 1 for flow chart.

Figure 3.1 Flow Diagram



3.4.2 Procedures

The study was approved by institutional review boards at all NAPLS-2 sites (*n*=8). All participants provided written informed consent, including parental consent. The work described in this article was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Trained raters conducted clinical assessments at baseline, 6, 12, 18, and 24 months, and neurocognition and social cognition at baseline, 12 and 24 months. Intraclass correlations for the total Scale of Psychosis-risk Symptoms (SOPS) scores were in the excellent range (range=0.82-0.93). [183]

3.4.3 Assessments

Negative symptoms were rated on the SOPS [36]. According to the NIMH-MATRICS negative symptom consensus the current domains of negative symptoms include asociality, anhedonia, avolition, blunted affect, and alogia [135]. Therefore, in the current study the SOPS negative symptoms were restricted to social anhedonia (N1), avolition (N2), and expression of emotion (N3), whereas experience of emotions and self (N4), ideational richness (N5), and occupational functioning (N6) were excluded.

To assess for functioning, two well-established scales were used, the Global Functioning: Social (GF:S) and the Global Functioning: Role (GF:R).[160,184] The GF:S assesses the level of social contact and friendships outside of the family unit. The GF:R assesses the level of role functioning at school or work. The GF:S and GF:R are rated on a 10-point scale, with higher scores representing higher functioning.

Neurocognition was assessed with nine MATRICS MCCB tests [185,186], including the Trail Making Test-Part A (TMT-A) [187], Symbol Coding from the Brief Assessment of

Cognition in Schizophrenia (SC-BACS) [188], Hopkins Verbal Learning Test-Revised immediate recall (HVLT-R) [189], Spatial Span subtest from the Wechsler Memory Scale-III (WMS-III SS) [190], Letter-Number Span (LNS)[191], Mazes subtest from the Neuropsychological Assessment Battery (NAB Mazes) [192], Brief Visuospatial Memory Test-Revised (BVMT-R) [193], Category Fluency (CF) [194], and the Continuous Performance Test-Independent Pairs (CPT-IP) [195].

For social cognition, to assess facial affect recognition the Penn Emotion Recognition (ER40) and the Penn Emotion Differentiation (EDF40) tasks were used [196,197]. Competence in relationship perception was assessed on the abbreviated Relationships Across Domains (RAD-45) [198,199]. To assess Theory of Mind (ToM), the Social Inference subscale of The Awareness of Social Inference Test (TASIT) was used [200].

As a proxy to defeatist beliefs, negative-self schemas (e.g., “I am a failure”) were assessed on the Brief Core Schema Scale (BCSS) [201], which is a 24-item self-report scale that assesses concerns about the self and others that has been validated in CHR samples [202]. Higher scores on the negative-self dimension represent increased maladaptive schemas. The BCSS negative-self schemas has similar items to the Dysfunctional Attitude Scale [203], which is commonly used to measure defeatist beliefs in schizophrenia research.

The Presence of Psychotic Symptoms (POPS) [204] criteria was utilized to determine transition to psychosis. Transition to psychosis required at least one of the five SOPS APS to reach a psychotic level of intensity (rating of 6) for a frequency of greater than or equal to 1 hour per day for 4 days per week during the past month or

that symptoms seriously impacted functioning (e.g., dangerous to self or others or severely disorganising).

To explore potential sources of secondary negative symptoms, depressive symptoms were assessed with the Calgary Depression Scale for Schizophrenia (CDSS) [205], which has been validated in CHR samples [206]. The SOPS APS subscale was utilized to measure APS.

3.4.4 Definition of persistent negative symptoms

PNS were defined as having one of the following three negative symptoms: social anhedonia (N1), avolition (N2), and expression of emotion (N3) based on the NIMH-MATRICS negative consensus on current domains of negative symptoms [135] scored ≥4 (i.e., moderately severe to extreme) for a duration of one year (i.e., scoring ≥4 at all 3 assessments: baseline, 6-months, and 12-months).

3.4.5 Analyses

Distributions of all variables were inspected using histograms, q-q plots, and Shapiro-Wilks tests before conducting statistical analysis. Participants were divided into two groups, the PNS group (N=67) versus the non-PNS group (N=673). Demographics were examined using chi-square analysis for categorical variables and independent samples t-test for continuous measures.

Generalized linear mixed models for repeated measures were utilized to examine changes over time (i.e., baseline, 6, 12, 18, and 24 months) between and within groups to accommodate for missing data and account for intra-participant correlations. All tests were adjusted for multiple comparisons using Tukey-Kramer, which remains conservative in the case of unequal sample sizes [207]. Participants with PNS were

compared with non-PNS participants over time on the GF:S, GF:R, BCSS negative-self schema subscale, MCCB, and social cognitive tests.

As an exploratory analysis we adjusted the PNS criteria to having moderately severe to extreme negative symptoms for a shorter period of six months, because most participants who transitioned to psychosis did so within the first year. Cox proportional hazards regression analysis was utilized to determine the differences in hazard rates between the PNS group and the non-PNS group in transitioning to psychosis.

In order to explore the impact of potential sources of secondary negative symptoms, participants with persistent depressive symptoms measured on the CDSS scored ≥7 for a duration of one year were excluded, and the above-mentioned analyses repeated, comparing the PNS with non-PNS participants over time on the GF:S, GF:R, BCSS negative-self schema subscale, MCCB, social cognitive tests, and transition. A CDSS score for a duration of one year was utilized to ensure that depressive symptoms were accounted for at the same time-points negative symptoms were measured (i.e., baseline, 6-months, and 12-months). A cut-off of ≥7 was chosen based on evidence that a score of at least a 7 on the CDSS yields high sensitivity and specificity in detecting depression in CHR individuals [208]. All statistical tests were 2-sided and an adjusted *P* value of < 0.05 was considered statistically significant. Analyses were performed using SAS version 9.2 [209].

3.5 Results

Seven hundred and forty CHR participants (424 males, 316 females) had sufficient negative symptom data at both baseline and follow-up (i.e., both 6 and 12-months), allowing for the distinction between groups (PNS vs non-PNS). Out of the 740

CHR participants, 67 (9.05%) had PNS and 673 (90.95%) did not. There were significantly more males (71.6% vs 55.9%) in the PNS group, see Table 1 for baseline demographics. The groups did not differ in current employment status, student status, and highest level of education at baseline. There were no significant differences between groups on APS rated on the SOPS or depressive symptoms measured on the CDSS at baseline, 6-months, 12-months, 18-months, and 24-months (See Supplementary Tables 1-2).

TABLE 3.1 Differences in Baseline Demographics Between Groups

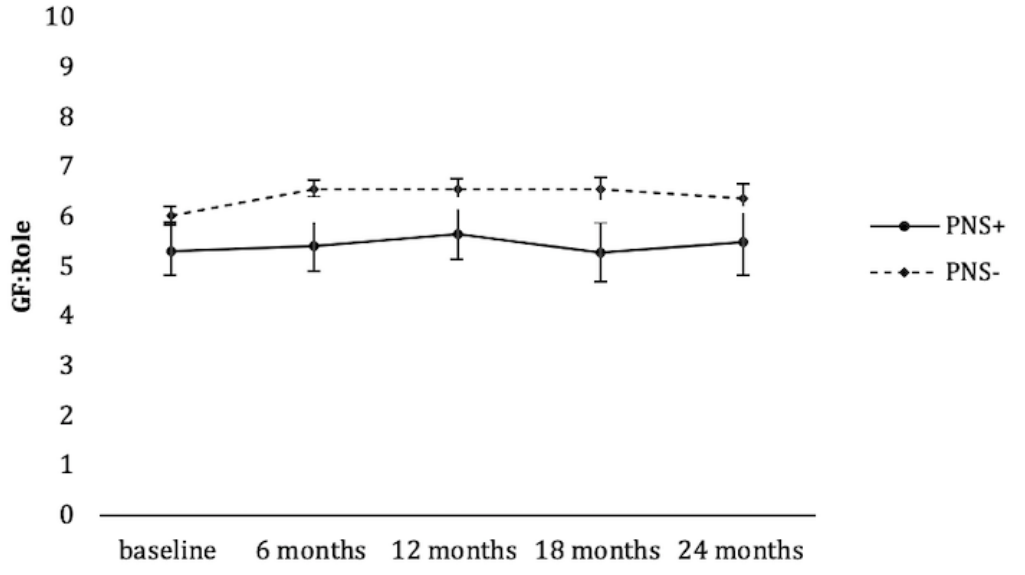
	Non-PNS	PNS	Test Statistic
	n = 673	*n* = 67	
Demographic Characteristic	*Mean (SD)*		*t*
Age in years	18.5 (4.28)	18.7 (4.04)	0.10
Years of education	11.3 (2.83)	11.5 (2.59)	0.33
Sex	*Number (%)*		X^2
Male	376 (55.9)	48 (71.6)	6.19*
Female	297 (44.1)	19 (28.4)	
Current living arrangement			
Living with family	508 (75.6)	53 (79.1)	7.04
Living with spouse/partner	37 (5.5)	1 (1.5)	
Living on own in apartment/house	32 (4.8)	7 (10.5)	
Living in group/rooming home	18 (2.7)	1 (1.5)	
Living with others, not spouse/partner	61 (9.1)	4 (6.0)	
Living in a shelter	2 (0.3)	0 (0.0)	
Other	14 (2.1)	1 (1.5)	
Currently working			
Yes	172 (25.6)	12 (17.9)	1.94
No	499 (74.4)	55 (82.1)	
Highest level of formal education obtained			
High school incomplete	352 (52.4)	37 (55.2)	1.24
High school graduate	260 (38.7)	22 (32.8)	
High school and above	60 (8.9)	8 (11.9)	
Currently enrolled as a student			
Yes	555 (82.6)	53 (79.1)	0.51
No	117 (17.4)	14 (20.9)	
	Mean† (SE)		*t*
Clinical Symptoms			
CDSS Total	5.7(0.18)	7.3(0.57)	0.20
SOPS Positive Symptom Total	11.9(0.15)	11.8(0.47)	-2.71
SOPS Negative Symptom Total	11.36(0.23)	17.18(0.54)	-7.78**
PNS Total (N1 +N2 + N3)	5.80(0.14)	9.76(0.28)	-9.07**

(*p<0.05; **p<0.001; *†represents the least squares means estimated by the generalized linear models for CDSS and SOPS Positive Symptom Total*). Abbreviations: CDSS= The Calgary Depression Scale for Schizophrenia; SD = standard deviation; SOPS = Scale of Psychosis-risk Symptoms; PNS = persistent negative symptoms

3.5.1 Changes in role functioning over time

Generalized linear mixed models for repeated measures were utilized to examine changes over time for GF:R, the models demonstrated that the PNS group had significantly poorer role functioning on the GF:R compared to the non-PNS group at 6-months (M=5.4, SEM=0.25, vs. M=6.5, SEM=0.09; $p<0.01$), 12-months (M=5.6, SEM=0.26 vs. M=6.5, SEM=0.10; $p<0.05$), and 18-months (M=5.3, SEM=0.31 vs. M=6.5, SEM=0.12; $p<0.01$), see Figure 2. Role functioning did not significantly improve over time compared to baseline within the PNS group, while role functioning within the non-PNS group significantly improved over time compared to baseline, with the exception of 24-months. After removing participants with persistent depressive symptoms, role functioning was significantly poorer in the PNS group (N=30) at 6,12,18, and 24-months compared to the non-PNS group [(N=182); See Supplementary Tables 3-4].

Figure 3.2 Differences between groups on Global Functioning: Role (GF:R) with 95% Confidence limits

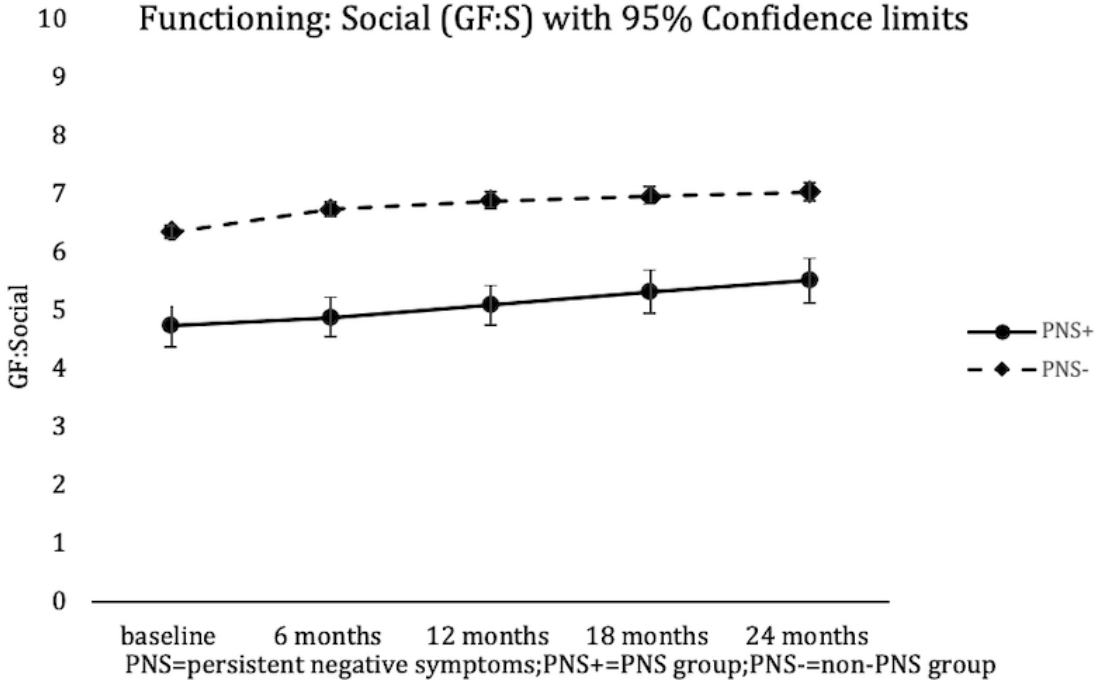


PNS=persistent negative symptoms;PNS+=PNS group;PNS-=non-PNS group

3.5.2 Changes in social functioning over time

Generalized linear mixed models for repeated measures were utilized to examine changes over time for GF:S, the PNS group had significantly poorer social functioning on the GF:S compared to the non-PNS group at baseline (M=4.7, SEM=0.18, vs. M=6.3, SEM=0.05; p<0.001), 6-months (M=4.9, SEM=0.18 vs. M=6.7, SEM=0.06; p<0.001), 12-months (M=5.1, SEM=0.17 vs. M=6.9, SEM=0.07; p<0.001), 18-months (M=5.3, SEM=0.19 vs. M=6.9, SEM =0.008; p<0.001), and 24-months (M=5.5, SEM=0.19 vs. M=7.00, SEM=0.08; p<0.001), see Figure 3. Social functioning did not significantly improve over time compared to baseline within the PNS group with the exception of 24-months, while social functioning within the non-PNS group significantly improved over time. After removing participants with persistent depressive symptoms, social functioning remained significantly poorer in the PNS group at all time points (Supplementary Tables 3-4).

Figure 3.3 Differences between groups on Global Functioning: Social (GF:S) with 95% Confidence limits



PNS=persistent negative symptoms;PNS+=PNS group;PNS-=non-PNS group

3.5.3 Changes in neurocognition over time

There were no significant differences between the PNS and non-PNS groups on the nine MCCB tests T-scores (i.e., TMT: Part A, BACS-SC, HVLT-R, WMS-III Spatial Span, LNS, NAB Mazes, BVMT-R, CF, and CPT-IP) at baseline, 12-months, or 24-months after adjusting for multiple comparisons (Table 2a and Table 2b), and after removing participants with persistent depressive symptoms (Supplementary Tables 5-6).

Table 3.2a. Differences in Cognitive Test Scores (*T-scores*) between groups

Cognitive Tests	Non-PNS (*n*=673)			PNS (*n*=67)		
	Mean (SE)					
	Baseline	12 months	24 months	Baseline	12 months	24 months
TMT: Part A	41.1(0.45)	44.3(0.59)	45.3(0.68)	42.9(1.42)	43.5(1.54)	46.4(1.73)
BACS Symbol Coding	41.0(0.56)	43.8(0.71)	44.6(0.76)	40.9(1.75)	45.6(1.92)	45.9(2.02)
HVLT-R	43.6(0.41)	45.3(0.53)	45.9(0.62)	44.6(1.29)	44.0(1.37)	45.7(1.58)
WMS-II Spatial Span	44.3(0.5)	45.6(0.59)	46.3(0.72)	44.1(1.54)	45.6(1.55)	45.7(1.84)
Letter-Number Span	43.1(0.46)	44.8(0.52)	45.9(0.58)	44.5(1.43)	45.2(1.41)	45.1(1.51)
NAB Mazes	42.2(0.42)	44.1(0.51)	45.1(0.60)	44.5(1.32)	45.5(1.34)	45.6(1.53)
BVMT-R	40.7(0.45)	41.3(0.57)	42.3(0.59)	39.9(1.41)	42.2(1.47)	42.3(1.49)
Category Fluency	48.3(0.45)	49.0(0.58)	49.9(0.68)	48.7(1.40)	50.8(1.48)	51.3(1.70)
CPT-IP	38.4(0.50)	41.2(0.58)	42.7(0.69)	38.4(1.54)	41.8(1.59)	41.7(1.79)

Abbreviations: Mean represents the least squares means estimated by the generalized linear model, SE represents the standard error of the mean; TMT = Trail Making Test; BACS = Brief Assessment of Cognition in Schizophrenia; HVLT-R = Hopkins Verbal Learning Test-Revised; WMS: Wechsler Memory Scale; NAB = Neuropsychological Assessment Battery; BVMT-R = Brief Visuospatial Memory Test-Revised; CPT-IP = Continuous Performance Test – Independent Pairs.

Table 3.2b. Differences in Cognitive Test Scores (*T-scores*) within groups

Cognitive Tests	Non-PNS (*n*=673)			PNS (*n*=67)		
	Mean (SE)					
	Baseline	12 months	24 months	Baseline	12 months	24 months
TMT: Part A	41.1(0.45)	44.3(0.59)a***	45.3(0.68)a***	42.9(1.42)	43.5(1.54)	46.4(1.73)
BACS Symbol Coding	41.0(0.56)	43.8(0.71)a***	44.6(0.76)a***	40.9(1.75)	45.6(1.92)a*	45.9(2.02)a*
HVLT-R	43.6(0.41)	45.3(0.53)a*	45.9(0.62)a**	44.6(1.29)	44.0(1.37)	45.7(1.58)
WMS-II Spatial Span	44.3(0.5)	45.6(0.59)	46.3(0.72)a*	44.1(1.54)	45.6(1.55)	45.7(1.84)
Letter-Number Span	43.1(0.46)	44.8(0.52)a**	45.9(0.58)a***	44.5(1.43)	45.2(1.41)	45.1(1.51)
NAB Mazes	42.2(0.42)	44.1(0.51)a**	45.1(0.60)a***	44.5(1.32)	45.5(1.34)	45.6(1.53)
BVMT-R	40.7(0.45)	41.3(0.57)	42.3(0.59)	39.9(1.41)	42.2(1.47)	42.3(1.49)
Category Fluency	48.3(0.45)	49.0(0.58)	49.9(0.68)	48.7(1.40)	50.8(1.48)	51.3(1.70)
CPT-IP	38.4(0.50)	41.2(0.58)a***	42.7(0.69)a***	38.4(1.54)	41.8(1.59)a*	41.7(1.79)

Abbreviations: Mean represents the least squares means estimated by the generalized linear model, SE represents the standard error of the mean; TMT = Trail Making Test; BACS = Brief Assessment of Cognition in Schizophrenia; HVLT-R = Hopkins Verbal Learning Test-Revised; WMS: Wechsler Memory Scale; NAB = Neuropsychological Assessment Battery; BVMT-R = Brief Visuospatial Memory Test-Revised; CPT-IP = Continuous Performance Test – Independent Pairs.
*Significance: a= significantly different from baseline; b= significantly different from 12 months; *p<0.05, **p<0.01, ***p<0.001*

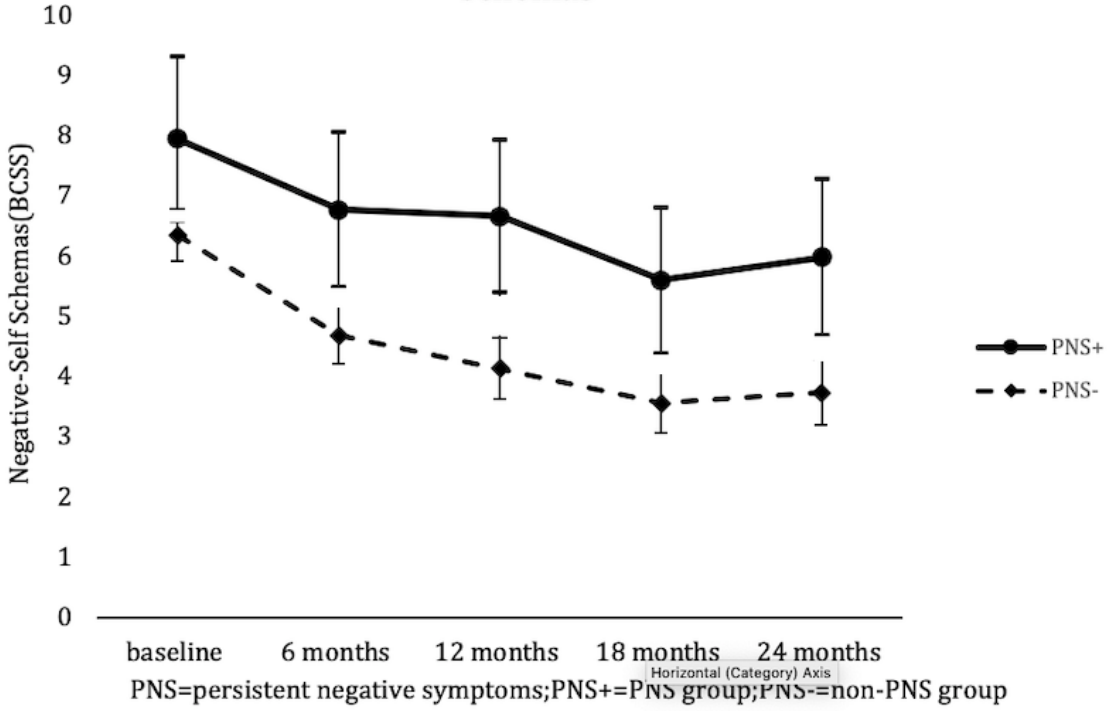
3.5.4 Changes in social cognition over time

There were no significant differences between the PNS and non-PNS groups on the five social cognition tasks (i.e., RAD-45 total, TASIT total, TASIT sarcasm, ER-40, and EDF40) at baseline, 12-months, and 24-months after adjusting for multiple comparisons (Supplementary Tables 7-8), and after removing participants with persistent depressive symptoms (Supplementary Tables 5-6).

3.5.6 Changes in negative-self schemas over time

Compared to the non-PNS group, PNS participants had significantly higher levels of total negative-self schemas at 12-months (M=6.7, SEM=0.64 vs. M=4.1, SEM=0.26; $p<0.05$) and 24-months (M=5.9, SEM=0.66 vs. M=3.7, SEM=0.27; $p<0.05$), with a trend level in significance for higher negative-self schemas in the PNS group at 6-months ($p=0.08$) and 18-months ($p=0.07$), see Figure 4. The non-PNS group significantly improved on total negative-self schemas at all time points compared to baseline, while the PNS group only significantly improved on total negative-self schemas at 18-months compared to baseline. After removing participants with persistent depressive symptoms, the significance between groups on negative-self schemas was lost (Supplementary Tables 3-4).

Figure 3.4 Differences between groups for Negative-Self Schemas



PNS=persistent negative symptoms;PNS+=PNS group;PNS-=non-PNS group

3.5.7 Transition to psychosis

To examine transition to psychosis the PNS criteria was adjusted to having moderately severe to extreme negative symptoms for a period of six months, as most participants who transitioned to psychosis did so within the first year. Using this criterion, 13 of the 139 participants in the PNS group developed psychosis (9.35%) compared to 80 of 601 in the non-PNS group (13.31%). In the Cox proportional hazards regression analysis, it appears that although the non-PNS group have a 77% (Hazard Ratio=1.77) increase in the hazard rate compared to those with PNS, this increase was not significant.

3.5.8 Proportion meeting PNS criteria over time

The proportion of CHR individuals meeting the 12-month PNS criterion declined over time from 9% (Baseline to 12-months), 7% (6-months to 18-months), to 4% (12-months to 24-months). Using the 6-month PNS criterion, a similar decline was observed from 19% (Baseline to 6-months), 10% (6-months to 12-months), 8% (12-months to 18-months), to 7% (18-months to 24-months).

3.6 Discussion

This paper examined the prevalence of PNS and their relationship with functioning, neurocognition, social cognition, negative-self schemas, and transition to psychosis. The results indicate that, in the NAPLS cohort, the prevalence of PNS is 9% when exercising a strict 12-month criteria. The PNS group demonstrated significantly more social and role deficits over time compared to the non-PNS group, which remained after controlling for persistent depressive symptoms. Both social and role deficits predominantly improved over time in the non-PNS group compared to baseline,

while the PNS group had worse functional deficits that remained relatively stable over two years. There were no differences between the groups on neurocognition and social cognition at any time point. When looking at negative-self schemas we found a trend for higher negative-self schemas over time in the PNS group, however when controlling for depressive symptoms these results were lost. Lastly, there were no significant differences between the groups on rates of transition to psychosis.

Consistent with our hypothesis, the PNS group had significant deficits in functioning over two years compared to the non-PNS group, controlling for persistent depressive symptoms. These results are supported by previous CHR studies that have shown a relationship between functional deficits and negative symptoms in CHR [126,157,164-167]. In the current study, the PNS group on average demonstrated serious impairment in social functioning (e.g., no close friends, and rarely seeking out others) whereas the non-PNS exhibited mild problems in social functioning (e.g., mild conflicts with peers). The same pattern was observed for role functioning, the PNS group on average demonstrated serious impairment in role functioning (e.g., failing multiple courses) whereas the non-PNS exhibited mild impairment in role functioning (e.g., frequently behind on tasks). Functioning was the main differentiating factor between groups in the current study, which emulates the functional deficits found in FEP with PNS [137-142].

Although these CHR youth have poorer neurocognition than healthy controls on the MCCB domains [210], our results do not support two previous CHR studies that demonstrated a significant relationship between negative symptoms and poor neurocognition [167,170]. One possible reason for this discrepancy is that in CHR studies

there are mixed results on neurocognition, in that more often than not CHR participants have poorer neurocognition than healthy controls but the results are not always consistent [169]. Alternatively, it is possible that neurocognition is poorer for those that transition to psychosis [163], though this relationship was not explored in the current analysis. Interestingly, in the current study the PNS group demonstrated a pattern of persistent poorer neurocognition on most MCCB tests, generally not improving over time compared to baseline, whereas neurocognition predominantly improved over time in the non-PNS group.

As expected, the PNS group did not differ in social cognition compared to the non-PNS group. These results are corroborated by other CHR studies that have not shown a relationship between social cognition and negative symptoms in CHR [173,174]. However, a recent review of FEP patients demonstrated that social cognitive deficits in FEP patients are associated with negative symptoms [211]. One possible explanation for the discrepancy between FEP and CHR samples is that social cognition in CHR is intermediary between healthy controls and FEP [173].

We found a trend for higher negative-self schemas over time in the PNS group, however when controlling for persistent depressive symptoms the between-group result was lost. This is contrary to a previous study where defeatist beliefs were associated with increased negative symptom severity [168]. This discrepancy may have arisen because we used a measure of negative-self schemas as a proxy for defeatist beliefs. In schizophrenia research, the Dysfunctional Attitude Scale (e.g., “If I fail at my work, then I am a failure as a person”) is commonly used to measure defeatist performance beliefs in which negative-self beliefs are explicitly linked to functional outcomes [203].

However, negative-self schemas (e.g., “I am worthless”) on the BCSS do not relate the negative-self beliefs explicitly to performance nor functional outcomes but rather to how an individual has generally viewed themselves over time. Nevertheless, the non-PNS group improved significantly at all time points on negative self-schemas, whilst the PNS group remained stable. To our knowledge no previous studies have used the BCSS scale as a proxy for defeatist beliefs, nor has negative self-schemas and defeatist beliefs been previously reported to capture the same construct. Future studies in CHR samples may wish to explore the convergent and discriminant validity between these two scales. Several secondary analyses (e.g., negative self-schemas) were not significantly different between the PNS and non-PNS groups after removing participants with persistent depressive symptoms, resulting in a small number of participants in the PNS group. Thus, it is possible that we were unable to detect a difference between the groups due to power constraints and an unbalanced sample size.

Contrary to our hypothesis, those with PNS did not have a significant risk of transition compared to the non-PNS group, which is consistent with one previous study [156]. With the current focus of identification and treatment of APS, and no treatments established to help negative symptoms nor functioning in CHR [162,212,213], an unfortunate trajectory emerges for CHR youth with PNS who may not be identified as needing services and thus do not receive the help they require. One possibility for future treatment of both functioning and negative symptoms in CHR is Cognitive Behavioral and Social Skills Training (CBSST), as findings suggest CBSST improves both functioning and negative symptoms in patients with schizophrenia [214]. Furthermore, preliminary data suggest that CBSST is a feasible treatment for CHR youth [215].

Other notable points are that the PNS group had significantly more males than the non-PNS group, which is consistent with prior research in CHR samples with more severe negative symptoms [155] and in FEP patients with PNS [142]. Secondly, we did not observe any differences on the CDSS nor the SOPS positive subscale between groups at any time-point. This may indicate that future PNS criteria in CHR may not require a cut-off or control for positive symptoms and depressive symptoms as has been required in schizophrenia and FEP studies. Next, the current study was unable to determine whether a particular negative symptom domain was driving PNS categorization as CHR participants could meet criteria for PNS even if the domains of negative symptom they scored changed between baseline and follow-up (e.g., anhedonia is elevated at baseline, and at 6 months only avolition is elevated). Lastly, the number of elevated negative symptom domains were not explored in the current study, however a previous PNS study in FEP demonstrated that certain negative symptom domains (i.e., amotivation) may play an important role in PNS categorization and the relationship with poor functional outcomes [138].

3.6.1 Strengths and Limitations

This study had the unique opportunity to explore PNS in the absence of frank psychotic symptoms in a large longitudinal cohort. However, several limitations should be considered when interpreting the results. First, due to the transient nature of symptoms in CHR samples we imposed a strict criterion of having at least moderately severe negative symptoms for a duration of one year to qualify for PNS. Utilizing such a strict definition of PNS possibly underestimated the prevalence of this phenomenon in CHR populations. Thus, a limitation of this study was using a 12-month PNS criteria to

determine prevalence. Selecting a specific timeframe criterion (i.e., 6 months vs 12 months) for PNS in CHR requires more consideration. One study found that the prevalence of PNS in a CHR sample to be 6.1% at baseline [156]. To compare our results, we utilized a less restrictive criteria of 6-months and the prevalence estimates of PNS in CHR doubled (19%), indicating that PNS are certainly evident even in CHR youth. These study results reflect similar results found in FEP patients where the PNS prevalence is between 27% to 13.2%, depending on definitions of PNS [138]. In this study the percentage of those meeting PNS criteria declined over time from baseline to 24-months, and as such negative symptoms may have declined.

In a similar vein another one of the limitations of the current study is that we chose a 12-month PNS criterion to look at the outcomes of functioning, neurocognition, and negative-self schemas, which may be of concern. One could consider employing a 6-month PNS criterion to examine outcomes and as such the results may differ. Thus, we re-ran the analyses by creating a PNS 6-month group with those who had negative symptoms for only a 6 month period and the only difference in the results between the two criteria on the primary outcomes of interest was that the groups now differed on GF:R at baseline and the BCSS at baseline and 18 months, with the PNS 6-month group having poorer ratings on these 2 measures. These results are presented in Supplementary Tables 9-12.

A third limitation was that the current study did not use the Buchanan criteria of PNS [136], as this criteria was developed for schizophrenia patients and FEP in clinical trials. The current study diverged from the Buchanan criteria by not defining a threshold for both positive symptoms/extrapyramidal symptoms plus having a longer duration of

one year. This is a CHR sample and compared to those with full-blown psychosis positive symptoms are attenuated and a defining feature of CHR criteria. Thus, an exclusion criterion within the PNS group based on a severity of APS was not imposed. Rather, since little is known about PNS in CHR samples we explored the relationship between PNS and APS by examining the differences between the groups over time and found no significant differences between groups at any time point. Due to differences in how PNS was operationalized (e.g., 6 months vs 12 months; negative symptom domains; cut-offs) it is possible that the current study measured something different than the Buchanan criteria of PNS.

A fourth limitation was that we followed the NIMH-MATRICS negative consensus on current domains of negative symptoms [135]. Due to the limitations of the SOPS in measuring negative symptoms we measured PNS in only four areas of negative symptoms asociality and anhedonia (i.e., social anhedonia), avolition, and expression of emotion, whereas no measure of alogia was employed. However, in FEP patients with PNS alogia has been measured and reported to be at significantly lower levels than other negative symptoms [138]. It may be that if improved CHR negative symptom scales are validated and aligned with the NIMH-MATRICS negative symptom domains, future studies could incorporate a more precise measure of PNS.

Lastly, although the SOPS negative symptom items may be limited the negative symptom scale on the SIPS has yet to be validated. However, the Prodromal Inventory of Negative Symptoms (PINS), a scale developed in accordance with the NIMH consensus conference recommendations demonstrated that the PINS total score was highly correlated with the SIPS negative symptom factor, signifying good convergent

validity [216]. In addition, the adapted version of the Brief Negative Symptom Scale (BNSS) for CHR youth demonstrated significant correlations between BNSS scores and the SIPS negative subscale score, further supporting convergent validity [217].

3.6.2 Directions for future research

The results of the current study may lead to several avenues for future research. First, future studies may wish to investigate other factors that may be related to PNS in CHR participants such as premorbid functioning, trauma, and quality of life to further improve the evidence base. Second, criteria should be further developed to reach consensus on how best to define PNS in CHR samples, not only to improve prevalence estimates but to establish consistent clinical sub-groups for targeted interventions. Third, no studies have examined the impact of any intervention on PNS. Thus, future trials may want to design interventions that are primarily geared towards impacting PNS.

3.6.3 Conclusions

PNS are prominent in individuals at CHR for psychosis, resulting in significant and persistent functional impairment. PNS remain even in CHR youth who do not convert to a full-blown psychotic disorder. Thus, PNS may represent an unmet therapeutic need in CHR populations for which there are currently no effective treatments.

3.7 Supplementary Material

Supplementary Table 1. Generalized linear models for changes over time between groups

	PNS (n=67)					Non-PNS (n=673)				
	Baseline	6 months	12 months	18 months	24 months	Baseline	6 months	12 months	18 months	24 months
Variable			**M* (SE)**					**M* (SE)**		
CDSS TOTAL	7.3(0.57)	5.3(0.53)	4.9(0.46)	4.5(0.53)	4.2(0.59)	5.7(0.18)	4.1(0.19)	3.4(0.19)	3.4(0.22)	3.4(0.24)
SOPS Positive Total	11.8(0.47)	9.1(0.55)	8.4(0.56)	7.1(0.61)	7.7(0.63)	11.9(0.15)	8.7(0.20)	7.9(0.22)	6.9(0.25)	6.8(0.25)

ST1 Note: *No differences between groups at any time point on any variable*

Supplementary Table 2. Generalized linear models for changes over time within groups

	PNS (n=67)					Non-PNS (n=673)				
	Baseline	6 months	12 months	18 months	24 months	Baseline	6 months	12 months	18 months	24 months
Variable			**M* (SE)**					**M* (SE)**		
CDSS TOTAL	7.3(0.57)	5.3(0.53)a*	4.9(0.46)a**	4.5(0.53)a***	4.2(0.59)a***	5.7(0.18)	4.1(0.19)a***	3.4(0.19)a***	3.4(0.22)a***	3.4(0.24)a***
SOPS Positive Total	11.8(0.47)	9.1(0.55)a***	8.4(0.56)a***	7.1(0.61)a***b***	7.7(0.63)a***	11.9(0.15)	8.7(0.20)a***	7.9(0.22)a***b**	6.9(0.25)a***b***c***	6.8(0.25)a*** b***c***

Supplementary Table 1 & 2: CDSS= The Calgary Depression Scale for Schizophrenia; M represents the least squares means estimated by the generalized linear models; PNS = persistent negative symptoms; SE represents the standard error of the mean; SOPS = Scale of Psychosis-risk Symptoms; a= significantly different from baseline; b= significantly different from 6 months; c= significantly different from 12 months; (*p<0.05, **p<0.01, ***p<0.001).*

Supplementary Table 3. Generalized linear models for changes over time within groups after removing participants with persistent depressive symptoms

	PNS (n=30)					Non-PNS (n=182)				
	Baseline	6 months	12 months	18 months	24 months	Baseline	6 months	12 months	18 months	24 months
Variable			**M* (SE)**					**M* (SE)**		
BCSS Negative-Self	4.71(0.79)	3.63(0.64)	4.10(0.68)	2.82(0.67)	3.98(0.69)	4.34(0.32)	2.96(0.26)a***	2.66(0.28)a***	2.34(0.28)a***	2.44(0.27)a***
GF:S	4.66(0.26)	5.03(0.23)	5.33(0.23)	5.49(0.24)	5.24(0.26)	6.76(0.10)	7.14(0.09)a***	7.30(0.09)a***	7.44(0.09)a***b**	7.40(0.10)a***
GF:R	5.80(0.37)	5.86(0.32)	5.76(0.35)	5.89(0.42)	5.00(0.51)	6.59(0.15)	7.25(0.13)a***	7.14(0.14)a**	6.93(0.17)	6.80(0.20)

Supplementary Table 4. Generalized linear models for changes over time between groups after removing participants with persistent depressive symptoms

	PNS (n=30)					Non-PNS (n=182)				
	Baseline	6 months	12 months	18 months	24 months	Baseline	6 months	12 months	18 months	24 months
Variable			**M* (SE)**					**M* (SE)**		
BCSS Negative-Self	4.71(0.79)	3.63(0.64)	4.10(0.68)	2.82(0.67)	3.98(0.69)	4.34(0.32)	2.96(0.26)	2.66(0.28)	2.34(0.28)	2.44(0.27)
GF:S	4.66(0.26)	5.03(0.23)	5.33(0.23)	5.49(0.24)	5.24(0.26)	6.76(0.10)a***	7.14(0.09)b***	7.30(0.09)c***	7.44(0.09)d***	7.40(0.10)e***
GF:R	5.80(0.37)	5.86(0.32)	5.76(0.35)	5.89(0.42)	5.00(0.51)	6.59(0.15)	7.25(0.13)b**	7.14(0.14)c*	6.93(0.17)d*	6.80(0.20)e*

Supplementary Table 3 & 4: Abbreviations: BCSS= Brief Core Schema Scale; GF:S= Global Functioning: Social; GF:R=Global Functioning: Role; M represents the least squares means estimated by the generalized linear models; PNS = persistent negative symptoms; SE represents the standard error of the mean; a= significantly different from baseline; b= significantly different from 6 months; c= significantly different from 12 months; d= significantly different from 18 months; e= significantly different from 24 months (*p<0.05, **p<0.01, ***p<0.001).*

Supplementary Table 5. Generalized linear models for changes in over time between groups after removing participants with persistent depressive symptoms

	PNS (n=30)			Non-PNS (n=182)		
	Baseline	12 months	24 months	Baseline	12 months	24 months
MCCB TESTS		**M* (SE)**			**M* (SE)**	
TMT: Part A	39.7(2.15)	41.3(2.33)	45.8(2.63)	41.2(0.85)	44.9(0.92)	45.9(1.04)
BACS Symbol Coding	40.4(2.95)	42.8(3.10)	42.2(3.06)	42.8(1.17)	45.8(1.23)	45.9(1.21)
HVLT-R	45.2(1.96)	42.7(2.09)	46.1(2.37)	45.0(0.77)	46.8(0.81)	48.2(0.94)
WMS-III Spatial Span	42.7(1.94)	45.4(2.28)	45.4(2.62)	45.7(0.77)	47.1(0.88)	47.7(1.03)
Letter-Number Span	42.3(2.11)	42.9(2.16)	45.7(2.15)	44.6(0.83)	45.9(0.84)	47.3(0.85)
NAB Mazes	45.8(1.92)	45.1(1.97)	44.1(2.45)	41.7(0.75)	43.5(0.78)	44.3(0.96)
BVMT-R	38.9(1.99)	40.8(2.19)	41.2(2.03)	41.9(0.78)	42.0(0.85)	43.3(0.80)
Category Fluency	47.8(2.08)	49.1(2.34)	51.0(2.71)	48.4(0.82)	49.3(0.91)	50.0(1.07)
CPT-IP	35.7(2.34)	38.6(2.46)	38.9(2.57)	39.4(0.93)	42.0(0.96)	43.6(1.01)
SOCIAL COGNITION		**M* (SE)**			**M* (SE)**	
RAD TOTAL	32.5(0.91)	34.4(1.02)	34.8(1.33)	31.8(0.37)	33.5(0.39)	33.8(0.52)
TASIT TOTAL SCORE	50.5(1.10)	55.2(1.13)	53.9(1.23)	52.6(0.43)	54.5(0.43)	55.4(0.47)
TASIT TOTAL SARCASM	24.8(0.73)	27.5(0.78)	27.7(0.86)	25.9(0.29)	26.9(0.30)	27.7(0.33)
ER40 CR	32.7(0.58)	34.1(0.65)	34.3(0.77)	32.9(0.23)	33.6(0.26)	34.4(0.32)
ED40 EDA	24.4(1.05)	23.4(1.22)	25.8(1.49)	24.9(0.42)	24.7(0.48)	25.1(0.62)

ST5 Note: *No differences between groups at any time point on any variable.*

Supplementary Table 6. Generalized linear models for changes over time within groups after removing participants with persistent depressive symptoms

		PNS (n=30)			Non-PNS (n=182)	
	baseline	12 Baseline	24 months	Baseline	12 months	24 months
MCCB TESTS		**M* (SE)**			**M* (SE)**	
TMT: Part A	39.7(2.15)	41.3(2.33)	45.8(2.63)	41.2(0.85)	44.9(0.92)a***	45.9(1.04)a***
BACS Symbol Coding	40.4(2.95)	42.8(3.10)	42.2(3.06)	42.8(1.17)	45.8(1.23)a**	45.9(1.21)a**
HVLT-R	45.2(1.96)	42.7(2.09)	46.1(2.37)	45.0(0.77)	46.8(0.81)	48.2(0.94)a**
WMS-III Spatial Span	42.7(1.94)	45.4(2.28)	45.4(2.62)	45.7(0.77)	47.1(0.88)	47.7(1.03)
Letter-Number Span	42.3(2.11)	42.9(2.16)	45.7(2.15)	44.6(0.83)	45.9(0.84)	47.3(0.85)a**
NAB Mazes	45.8(1.92)	45.1(1.97)	44.1(2.45)	41.7(0.75)	43.5(0.78)	44.3(0.96)
BVMT-R	38.9(1.99)	40.8(2.19)	41.2(2.03)	41.9(0.78)	42.0(0.85)	43.3(0.80)
Category Fluency	47.8(2.08)	49.1(2.34)	51.0(2.71)	48.4(0.82)	49.3(0.91)	50.0(1.07)
CPT-IP	35.7(2.34)	38.6(2.46)	38.9(2.57)	39.4(0.93)	42.0(0.96)a***	43.6(1.01)a***
SOCIAL COGNITION		**M* (SE)**			**M* (SE)**	
RAD TOTAL	32.5(0.91)	34.4(1.02)	34.8(1.33)	31.8(0.37)	33.5(0.39)a***	33.8(0.52)a***
TASIT TOTAL SCORE	50.5(1.10)	55.2(1.13)a***	53.9(1.23)a*	52.6(0.43)	54.5(0.43)a***	55.4(0.47)a***
TASIT TOTAL SARCASM	24.8(0.73)	27.5(0.78)a***	27.7(0.86)a**	25.9(0.29)	26.9(0.30)a***	27.7(0.33)a***
ER40 CR	32.7(0.58)	34.1(0.65)	34.3(0.77)	32.9(0.23)	33.6(0.26)	34.4(0.32)a***
ED40 EDA	24.4(1.05)	23.4(1.22)	25.8(1.49)	24.9(0.42)	24.7(0.48)	25.1(0.62)

*Supplementary Table 5 & 6: Abbreviations: Mean represents the least squares means estimated by the generalized linear model, SE represents the standard error of the mean; TMT = Trail Making Test; BACS = Brief Assessment of Cognition in Schizophrenia; HVLT-R = Hopkins Verbal Learning Test-Revised; WMS: Wechsler Memory Scale; NAB = Neuropsychological Assessment Battery; BVMT-R = Brief Visuospatial Memory Test-Revised; CPT-IP = Continuous Performance Test – Independent Pairs. ER40= Penn Emotion Recognition Task; ED40= Penn Emotion Differentiation task; PNS = persistent negative symptoms; RAD= Relationships Across Domains; SE represents the standard error of the mean; TASIT= The Awareness of Social Inference Test; a= significantly different from baseline; b= significantly different from 6 months; c= significantly different from 12 months; (*p<0.05, **p<0.01, ***p<0.001).*

Supplementary Table 7. Generalized linear models for changes in social cognition over time between groups

		PNS (n=67)			Non-PNS (n=673)	
	Baseline	12 months	24 months	Baseline	12 months	24 months
Variable		**M* (SE)**			**M* (SE)**	
RAD TOTAL	32.7(0.67)	33.8(0.74)	34.9(0.88)	31.5(0.22)	32.9(0.28)	33.8(0.34)
TASIT TOTAL SCORE	51.9(0.77)	54.7(0.78)	55.3(0.81)	52.4(0.25)	54.2(0.29)	55.1(0.31)
TASIT TOTAL SARCASM	25.5(0.49)	27.2(0.54)	28.3(0.58)	25.7(0.16)	26.7(0.2)	27.4(0.23)
ER40 CR	32.7(0.44)	33.4(0.49)	33.9(0.55)	32.8(0.14)	33.5(0.19)	34.0(0.23)
ED40 EDA	24.6(0.75)	24.7(0.82)	24.9(1.02)	24.2(0.25)	24.3(0.33)	24.6(0.42)

ST7 Note: *No differences between groups at any time point on any variable.*

Supplementary Table 8. Generalized linear models for changes in social cognition over time within groups

		PNS (n=67)			Non-PNS (n=673)	
	baseline	12 Baseline	24 months	Baseline	12 months	24 months
Variable		**M* (SE)**			**M* (SE)**	
RAD TOTAL	32.7(0.67)	33.8(0.74)	34.9(0.88)a*	31.5(0.22)	32.9(0.28)a***	33.8(0.34)a***b*
TASIT TOTAL SCORE	51.9(0.77)	54.7(0.78)a***	55.3(0.81)a***	52.4(0.25)	54.2(0.29)a***	55.1(0.31)a***b*
TASIT TOTAL SARCASM	25.5(0.49)	27.2(0.54)a**	28.3(0.58)a***	25.7(0.16)	26.7(0.2)a***	27.4(0.23)a***b*
ER40 CR	32.7(0.44)	33.4(0.49)	33.9(0.55)	32.8(0.14)	33.5(0.19)a**	34.0(0.23)a***
ED40 EDA	24.6(0.75)	24.7(0.82)	24.9(1.02)	24.2(0.25)	24.3(0.33)	24.6(0.42)

Supplementary Table 7 & 8: ER40= Penn Emotion Recognition Task; ED40= Penn Emotion Differentiation task; M* represents the least squares means estimated by the generalized linear models; PNS = persistent negative symptoms; RAD= Relationships Across Domains; SE represents the standard error of the mean; TASIT= The Awareness of Social Inference Test; a= significantly different from baseline; b= significantly different from 6 months; c= significantly different from 12 months; (*p<0.05, **p<0.01, ***p<0.001).

Supplementary Table 9. Generalized linear models using 6-month PNS criteria between groups on outcomes of interest

	Non-PNS (n=601)					*PNS (n=139)*				
	Baseline	**6 months**	**12 months**	**18 months**	**24 months**	**Baseline**	**6 months**	**12 months**	**18 months**	**24 months**
Variable			M* (SE)					M* (SE)		
BCSS Negative-Self	6.1(0.23)	4.3(0.26)	3.9(0.27)	3.3(0.27)	3.4(0.28)	7.9(0.48)a*	6.7(0.44)b***	6.2(0.50)c**	5.4(0.48)d**	6.0(0.51)e***
GFS_CURRENT	6.5(0.06)	6.9(0.06)	6.9(0.07)	7.1(0.08)	7.1(0.08)	5.1(0.12)a***	5.2(0.11)b***	5.6(0.13)c***	5.7(0.15)d***	5.8(0.15)e***
GFR_CURRENT	6.1(0.08)	6.8(0.09)	6.7(0.10)	6.6(0.13)	6.4(0.14)	5.2(0.18)a***	5.2(0.16)b***	5.6(0.19)c***	5.4(0.24)d***	5.6(0.27)

Supplementary Table 10. Generalized linear models using 6-month PNS criteria within groups on outcomes of interest

	Non-PNS (n=601)					*PNS (n=139)*				
	Baseline	**6 months**	**12 months**	**18 months**	**24 months**	**Baseline**	**6 months**	**12 months**	**18 months**	**24 months**
Variable			M* (SE)					M* (SE)		
BCSS Negative-Self	6.1(0.23)	4.3(0.26)a***	3.9(0.27)a***	3.3(0.27)a***b**	3.4(0.28)a***	7.9(0.48)	6.7(0.44)	6.2(0.50)a*	5.4(0.48)a***	6.0(0.51)a*
GFS_CURRENT	6.5(0.06)	6.9(0.06)a***	6.9(0.07)a***	7.1(0.08)a***	7.1(0.08)a***	5.1(0.12)	5.2(0.11)	5.6(0.13)a**b*	5.7(0.15)a**b**	5.8(0.15)a***b***
GFR_CURRENT	6.1(0.08)	6.8(0.09)a***	6.7(0.10)a***	6.6(0.13)a**	6.4(0.14)	5.2(0.18)	5.2(0.16)	5.6(0.19)	5.4(0.24)	5.6(0.27)

Supplementary Table 9 & 10: Abbreviations: BCSS= Brief Core Schema Scale; GF:S= Global Functioning: Social; GF:R=Global Functioning: Role; M represents the least squares means estimated by the generalized linear models; PNS = persistent negative symptoms; SE represents the standard error of the mean; a= significantly different from baseline; b= significantly different from 6 months; c= significantly different from 12 months; d= significantly different from 18 months; e= significantly different from 24 months (*p<0.05, **p<0.01, ***p<0.001).*

Supplementary Table 11. Generalized linear models using 6-month PNS criteria between groups on neurocognition and social cognition

	Non-PNS (n=601)			PNS (n=139)		
	Baseline	12 months	24 months	Baseline	12 months	24 months
Variable		M* (SE)			M* (SE)	
RAD Total	31.6(0.22)	32.8(0.28)	33.5(0.35)	31.8(0.46)	33.3(0.57)	35.1(0.69)
TASIT Total	52.4(0.26)	54.1(0.30)	55.1(0.32)	52.0(0.53)	54.7(0.60)	55.0(0.64)
TASIT Total Sarcasm	23.6(0.19)	26.2(0.24)	27.9(0.26)	23.4(0.40)	27.6(0.48)	28.4(0.52)
ER40 CR	32.8(0.15)	33.2(0.15)	33.3(0.15)	32.4(0.31)	32.6(0.31)	32.7(0.31)
EDF40 EDA	24.2(0.25)	24.2(0.26)	24.3(0.26)	24.1(0.52)	24.3(0.53)	24.2(0.52)
TMT: Part A	41.3(0.48)	44.8(0.61)	45.6(0.70)	41.1(0.98)	41.6(1.21)	44.9(1.38)
BACS-SC	41.5(0.60)	44.1(0.75)	45.1(0.80)	38.8(1.21)	43.7(1.48)	43.6(1.57)
HVLT-R	44.0(0.44)	45.6(0.55)	46.0(0.65)	42.7(0.890	43.1(1.1)	45.1(1.27)
WMS-III Spatial Span	44.8(0.53)	45.9(0.61)	46.3(0.75)	42.2(1.06)	44.4(1.220	45.4(1.47)
Letter-Number Span	43.3(0.49)	45.0(0.54)	45.9(0.61)	42.5(0.99)	44.1(1.08)	44.9(1.20)
NAB Mazes	42.5(0.45)	44.3(0.54)	45.1(0.62)	42.3(0.91)	44.4(1.06)	45.2(1.22)
BVMT-R	40.7(0.48)	41.6(0.59)	42.6(0.61)	40.3(0.97)	41.1(1.18)	41.5(1.20)
Category Fluency	48.8(0.48)	49.2(0.61)	50.3(0.70)	48.1(0.97)	49.5(1.19)	49.5(1.38)
CPT-IP	38.8(0.53)	41.6(0.61)	43.2(0.71)	37.0(1.06)	40.0(1.21)	40.1(1.42)

ST11 Note: *No differences between groups at any time point on any variable.*

Supplementary Table 12. Generalized linear models using 6-month PNS criteria within groups on neurocognition and social cognition

		Non-PNS (n=601)			**PNS (n=139)**	
	Baseline	12 months	24 months	Baseline	12 months	24 months
Variable		M* (SE)			M* (SE)	
RAD Total	31.6(0.22)	32.8(0.28)a***	33.5(0.35)a***	31.8(0.46)	33.3(0.57)a*	35.1(0.69)a***b*
TASIT Total	52.4(0.26)	54.1(0.30)a***	55.1(0.32)a***b**	52.0(0.53)	54.7(0.60)a***	55.0(0.64)a***
TASIT Total Sarcasm	23.6(0.19)	26.2(0.24)a***	27.9(0.26)a***b***	23.4(0.40)	27.6(0.48)a***	28.4(0.52)a***
ER40 CR	32.8(0.15)	33.2(0.15)a**	33.3(0.15)a***	32.4(0.31)	32.6(0.31)	32.7(0.31)
EDF40 EDA	24.2(0.25)	24.2(0.26)	24.3(0.26)	24.1(0.52)	24.3(0.53)	24.2(0.52)
TMT: Part A	41.3(0.48)	44.8(0.61)a***	45.6(0.70)a***	41.1(0.98)	41.6(1.21)	44.9(1.38)a*
BACS-SC	41.5(0.60)	44.1(0.75)a***	45.1(0.80)a***	38.8(1.21)	43.7(1.48)a***	43.6(1.57)a**
HVLT-R	44.0(0.44)	45.6(0.55)a*	46.0(0.65)a*	42.7(0.890	43.1(1.1)	45.1(1.27)
WMS-III Spatial Span	44.8(0.53)	45.9(0.61)	46.3(0.75)	42.2(1.06)	44.4(1.220	45.4(1.47)
Letter-Number Span	43.3(0.49)	45.0(0.54)a**	45.9(0.61)a***	42.5(0.99)	44.1(1.08)	44.9(1.20)
NAB Mazes	42.5(0.45)	44.3(0.54)a**	45.1(0.62)a***	42.3(0.91)	44.4(1.06)	45.2(1.22)
BVMT-R	40.7(0.48)	41.6(0.59)	42.6(0.61)a*	40.3(0.97)	41.1(1.18)	41.5(1.20)
Category Fluency	48.8(0.48)	49.2(0.61)	50.3(0.70)	48.1(0.97)	49.5(1.19)	49.5(1.38)
CPT-IP	38.8(0.53)	41.6(0.61)a***	43.2(0.71)a***	37.0(1.06)	40.0(1.21)a*	40.1(1.42)

*Supplementary Table 11 & 12: Abbreviations: Mean represents the least squares means estimated by the generalized linear model, SE represents the standard error of the mean; TMT = Trail Making Test; BACS = Brief Assessment of Cognition in Schizophrenia; HVLT-R = Hopkins Verbal Learning Test-Revised; WMS: Wechsler Memory Scale; NAB = Neuropsychological Assessment Battery; BVMT-R = Brief Visuospatial Memory Test-Revised; CPT-IP = Continuous Performance Test – Independent Pairs. ER40= Penn Emotion Recognition Task; ED40= Penn Emotion Differentiation task; PNS = persistent negative symptoms; RAD= Relationships Across Domains; SE represents the standard error of the mean; TASIT= The Awareness of Social Inference Test; a= significantly different from baseline; b= significantly different from 12 months (*p<0.05, **p<0.01, ***p<0.001)*

Chapter 4: Negative Symptoms and Functioning in Youth at Risk of Psychosis: A Systematic Review and Meta-Analysis

4.1 Preface

Research presented as part of this chapter is currently under review as; Daniel Devoe; Amy Braun; Thomas Seredynski, Jean Addington (Under Review). *Negative Symptoms and Functioning in Youth at Risk of Psychosys.* Harvard Review of Psychiatry

Author Contributions: DD was involved in the overall concept of the paper, writing, and meta-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.

The only alterations made to this publication were for thesis formatting.

4.2 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.

4.3 Introduction

Negative symptoms are a significant cause of burden to both patients with schizophrenia and health-care systems.[134,135] Furthermore, negative symptoms are often associated with functional deficits in patients with schizophrenia,[218,219] with both negative symptoms and functional deficits present long before the onset of a first episode.[220,221] Evidence also suggests that specific negative symptom domains, such as avolition, may play a role in predicting functional outcomes in schizophrenia.[222] Over the past decade these associations have generated more interest in negative symptoms, such that both negative symptoms and functioning have become primary targets in the development of new treatments for individuals with psychosis.[134] Likewise, those at clinical high risk (CHR) for psychosis have both negative symptoms and functional deficits,[144,145,223] in fact, one large review demonstrated that the prevalence of negative symptoms in CHR youth is higher than that of first episode patients (FEP).[224] 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.[225]

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.[223] In addition, CHR youth present with a wide range of negative symptom domains such as flat affect, alogia, anhedonia, avolition, and asociality.[226,227] Similar to those with schizophrenia, CHR youth also present with deficits in global functioning,[228] deficits in social functioning,[229] and deficits in role functioning and employment when compared to their non-psychiatric peers.[229]

Moreover, one study suggested that difficulties in social and role functioning in CHR youth were equivalent to those observed in first-episode psychosis patients.[230] Both negative symptoms and functioning have been shown to reduce quality of life and impact long-term outcomes in CHR individuals,[47-50] 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.

4.4 Method

4.4.1 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) guidelines [231] and preferred reporting for systematic reviews and meta-analyses (PRISMA).[58,60]

4.4.2 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.[232] 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.

4.4.3 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; (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 reconciled in an iterative approach.

4.4.4 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 ± SD), number of males/percent male, negative symptom scores (mean ± 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).

4.4.5 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.[233] 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. Studies were not excluded from this systematic review and meta-analysis based on the quality assessments.

4.4.6 Data Synthesis and Analysis

Due to heterogeneity between studies, DerSimonian and Laird [73] 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.[234] 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=>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 $d=2r/[\sqrt{(1-r_2)}]$ 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.[235] Next, in one study the reported R_2 was converted to *r* from a stepwise regression model[236] and the *t*-value in an ANOVA from another study was transformed into *r,* [237] 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-MATRICS five negative symptom domains, which include asociality, anhedonia, avolition, blunted affect, and alogia [135].

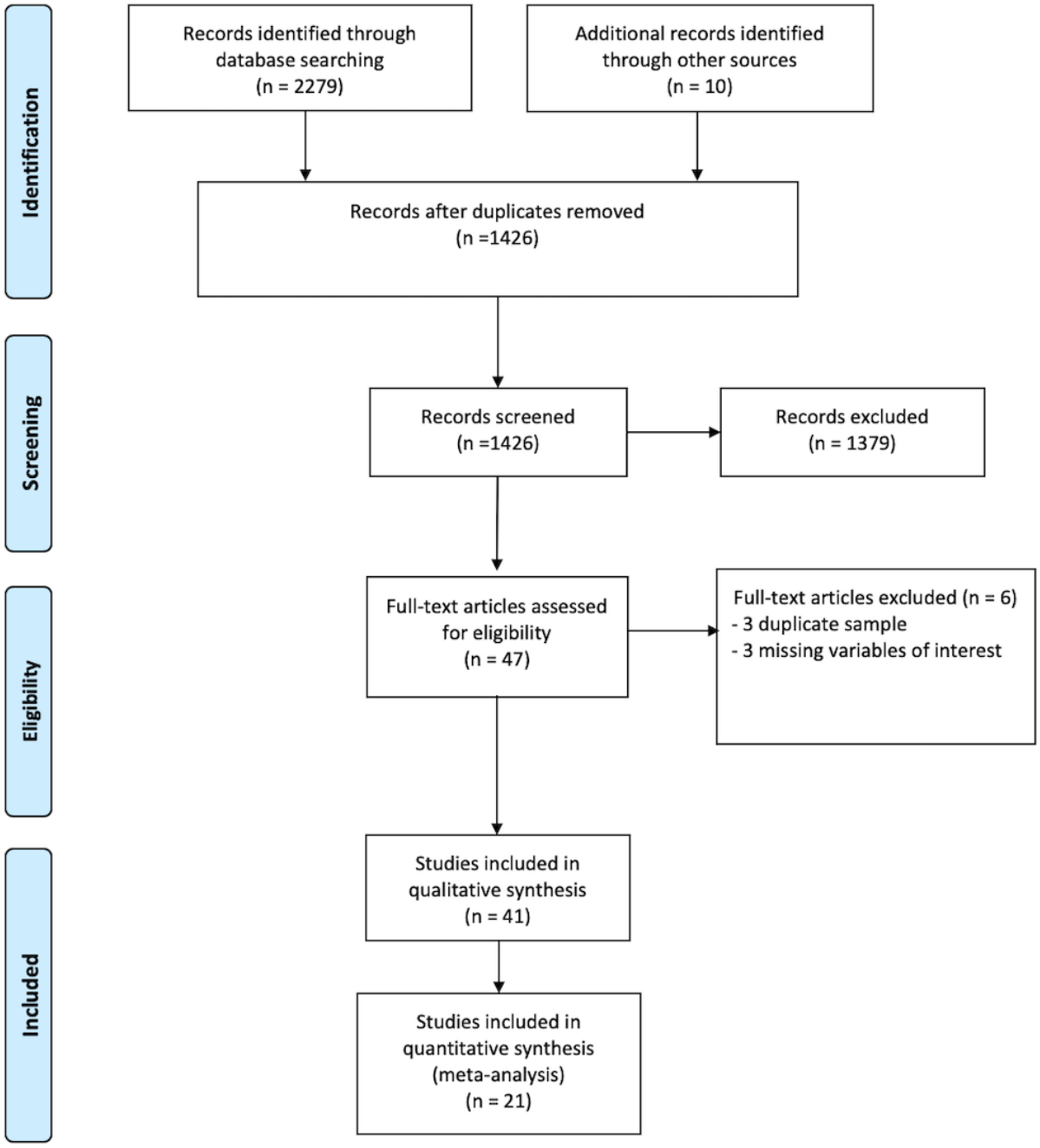
For publication bias, funnel plots were stratified by associations, at least 10 studies were required to visually assess funnel plots for asymmetry[238] and publication bias in these cases was further explored using Egger's test for asymmetry.[239] Statistical heterogeneity was examined using the I^2 statistic, with $I^2 \geq 50\%$ deemed moderate, and $I^2 \geq 75\%$ high heterogeneity. All analyses were performed in STATA (v.13).[240]

4.5 Results

4.5.1 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 (κ=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 4.1.

Figure 4.1 PRISMA Flow Diagram



4.5.2 Meta-Analysis Study and Participant Characteristics

Studies included in the meta-analysis portion of this review are described in Table 4.1, most studies were conducted in North America (n=9),[160,241-248] followed by Asia (n=5),[230,249-252] Europe (n=4),[236,237,253,254] and Australia (n=3).[255-257] 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%.

Table 4.1 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.	Cornblatt 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
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.	Glenthoj 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

4.5.3 Risk-of-Bias

Studies included in the meta-analyses were assessed with the Downs and Black instrument (Table 4.2a and Table 4.2b). For cross-sectional studies, the average Downs and Black score was 14.64/15, indicating relatively good quality across studies. For longitudinal studies, the average Downs and Black score was 15/17, indicating relatively good quality across studies as well.

Table 4.2a 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	13.Standard facilities	16.Data dredging	18.Statistics testing	20.Accurate measures	25.Confond adjustment	**TOTAL**
1.	Corcoran et al. (2011)	1	1	1	2	1	1	1	1	1	1	1	1	1	1	15
2.	Cotter et al., (2017)	1	1	1	0	1	1	1	1	1	1	1	1	1	0	12
3.	Cressman et al., (2015)	1	1	1	2	1	1	1	1	1	1	1	1	1	1	15
4.	Dominguez-Martinez et al., (2015)	1	1	1	2	1	1	1	1	1	1	1	1	1	1	15
5.	Fulford et al., (2013)	1	1	1	2	1	1	1	1	1	1	1	1	1	1	15
6.	Gur et al. (2015)	1	1	1	2	1	1	1	1	1	1	1	1	1	1	15
7.	Kim et al. (2013)	1	1	1	2	1	1	1	1	1	1	1	1	1	1	15
8.	Lee et al., (2017)	1	1	1	2	1	1	1	1	1	1	1	1	1	1	15
9.	Niendam et al., (2006)	1	1	1	2	1	1	1	1	1	1	1	1	1	1	15
10.	Robustelli et al., (2018)	1	1	1	2	1	1	0	1	1	1	1	1	1	1	14
11.	Seo et al., (2018)	1	1	1	2	1	1	1	1	1	1	1	1	1	0	14
12.	Shim et al. (2008)	1	1	1	2	1	1	1	1	1	1	1	1	1	1	15
13.	Svirskis et al., (2007)	1	1	1	2	1	1	1	1	1	1	1	1	1	1	15
14.	Glenthoj et al., (2016)	1	1	1	2	1	1	1	1	1	1	1	1	1	1	15
	TOTAL	14	14	14	26	14	14	13	14	14	14	14	14	14	12	

Table 2a 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 4.2b Quality assessment checklist for longitudinal studies included in meta-analysis (k=7).

Table 2b Notes: "1" = Yes; "0" = No; "2" = Q5 Confounders listed and described in this sample; "–" = Unable to determine and counts as 0. *Questions*

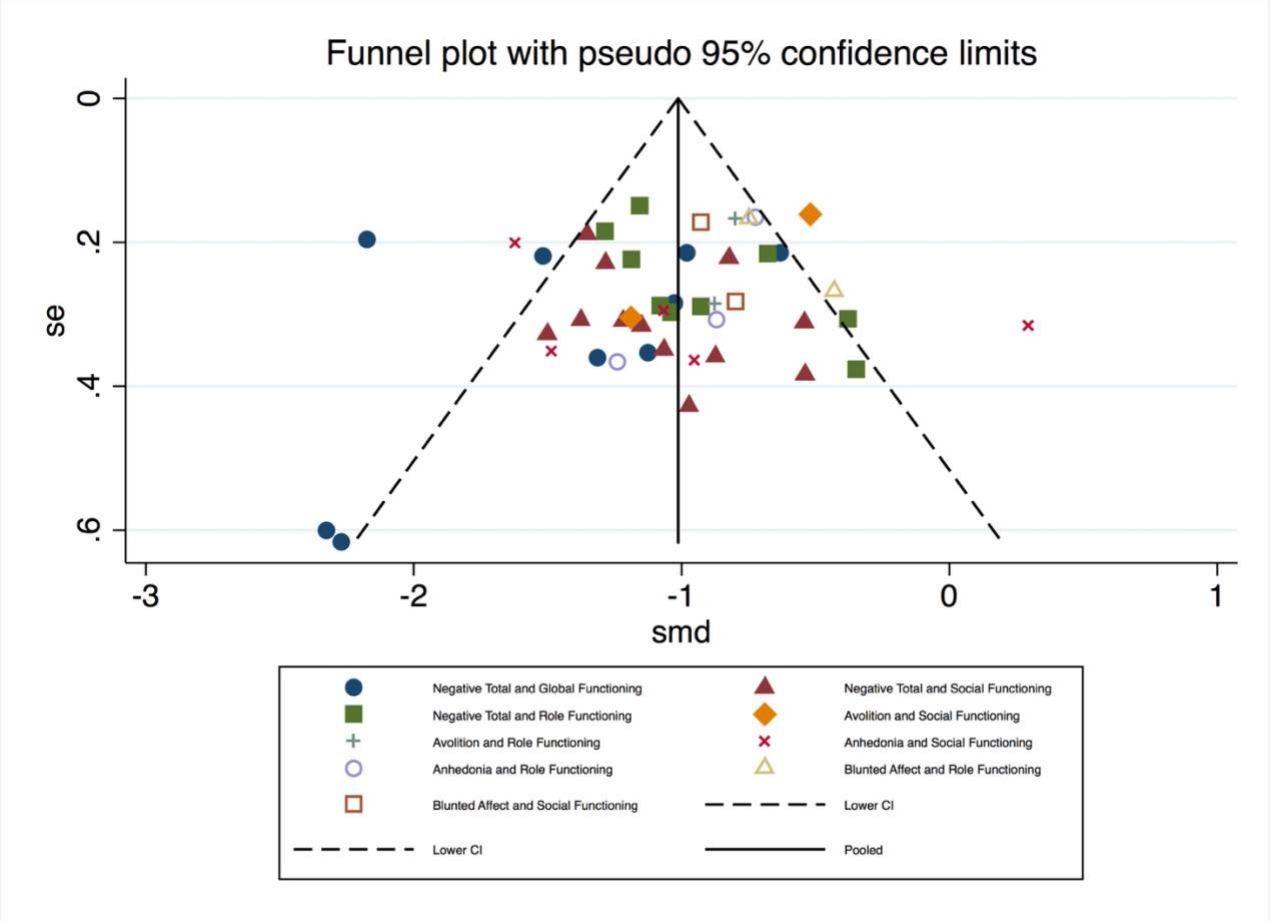
Study		1.Aims	2.Measures	3.Characteristics	5.Confonders	6.Findings	7.Random variability	9.Lost to follow –up	10.Probabilities	11.Representative sample	12.Representative accepted	13.Standard facilities	16.Data dredging	18.Statistics	20.Accurate measures	25.Confound adjustment	26.Losses to follow –up	**TOTAL**
1.	Cornblatt et al., (2007)	1	1	1	2	1	1	0	1	1	1	1	1	1	1	1	-	15
2.	Lin et al., (2013)	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	0	13
3.	Meyer et al. (2014)	1	1	1	2	1	1	1	1	1	1	1	1	1	1	1	-	16
4.	Pelizza et al., (2019)	1	1	1	2	1	1	0	1	1	1	1	1	1	1	1	0	15
5.	Shin et al. (2016)	1	1	1	2	1	1	0	1	1	1	1	1	1	1	1	0	15
6.	Willhite et al., (2009)	1	1	1	2	1	1	1	1	1	1	1	1	1	1	1	1	17
7.	Cotter et al., (2016)	1	1	1	2	1	1	0	1	1	1	1	1	1	1	-	-	14
	TOTAL	7	7	7	13	7	7	2	7	7	7	7	7	7	7	5	1	

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.

4.5.4 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).

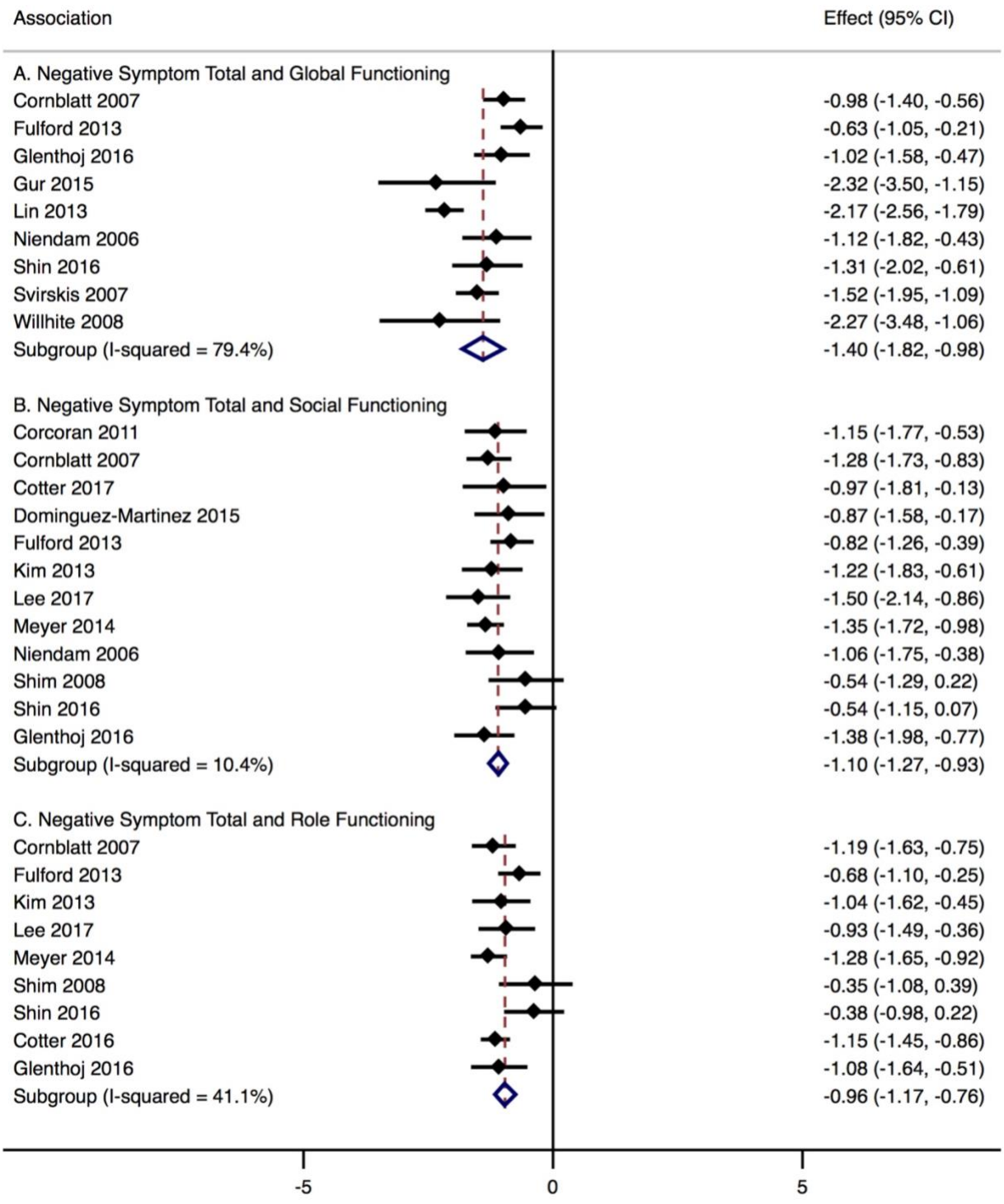
Figure 4.2 Funnel Plot Stratified by Association



4.5.5 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; I^2=79.4%; *P*<0.001, 9 studies, N=782; Figure 3a), social functioning (*d*, -1.10; 95% CI= -1.27, -0.93; I^2=10.4%; *P*<0.001, 12 studies, N=811; Figure 3b), and role functioning (*d*, -0.96; 95% CI= -1.17, -0.76; I^2=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.[258]

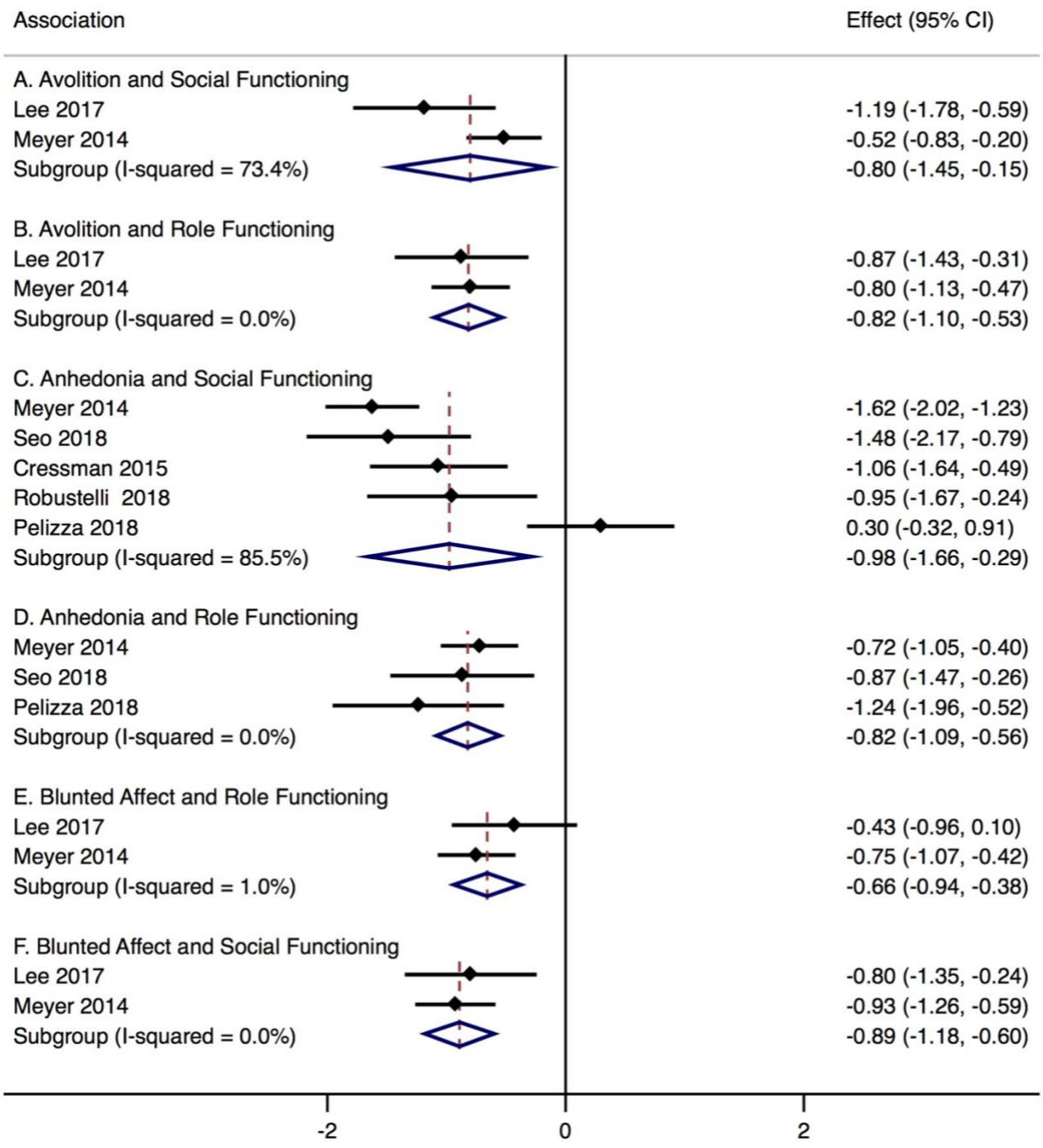
Figure 4.3 Negative Symptom Total and Functioning Forest Plots



4.5.6 Avolition and Functioning

Avolition was significantly associated with poorer social functioning (*d*, -0.80; 95% CI= -1.45, -0.15; I^2=73.4%; *P*<0.05, 2 studies, N=228) and role functioning (*d*, -0.82; 95% CI= -1.10, -0.53; 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; *P*<0.001, 1 study, N=110).[259]

Figure 4.4 Negative Symptom Domains and Functioning Forest Plots



4.5.7 Anhedonia and Functioning

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

4.5.8 Blunted affect and Functioning

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

4.5.9 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.

4.5.9.1 Negative Symptoms and Premorbid Functioning

Four studies looked at the relationship between premorbid functioning and negative symptoms. Two studies demonstrated that premorbid social maladjustment was associated with social anhedonia and reduced expression of emotion [260,261] and in another study poor premorbid social adjustment predicted less improvement in negative symptoms.[262] The fourth study showed that poorer premorbid functioning was significantly correlated with both increased negative symptom severity and poorer functioning.[263]

4.5.9.2 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.[264] Second, another study demonstrated that a poor outcome group had higher negative symptoms and lower functioning compared to a good outcome group.[265] 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.[144] Next, one study demonstrated that a negative symptom only group had an increased risk of functional disability relative to a positive symptom group,[266] 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.[267] 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.[268]

4.5.9.3 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 functioning[269] while in another study the relationship between the personality trait interpersonal sensitivity and social functioning was not mediated by negative symptoms.[270] Next, a factor analysis indicated a two factor model consisting of two

negative symptom dimensions of volition and emotion.[227] 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).[271]

4.5.9.4 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 functioning [272] while another study showed that anhedonia-asociality, attention disturbances, and disorder of thought content predicted poorer functioning.[273] Next, a combination of increased negative symptoms and reduced performance on a verbal recall task was the best predictor of poor functional outcome.[265] Other studies have shown that having longer negative symptom duration predicted poor social functioning[274] and that negative symptom severity uniquely predicted poor social functioning.[166]

4.6 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.[137-142,218,219] 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.[275] Thus, it is possible that CHR youth with negative symptoms and functional deficits may not be identified as needing clinical services and therefore may not receive the help they require.

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.[276-279] 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, [222,280-282] anhedonia and functional outcomes,[283-285] and blunted affect and functional outcomes.[286] 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.[166] 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.[287,288] 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 [289-291] and in some cases negative symptoms demonstrate a stronger risk factor for lower functioning than positive psychotic symptoms in schizophrenia.[290] 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.[274] 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.

4.6.1 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) [36] negative symptom scale was the most commonly used measure for negative symptoms in this review. According to researchers,[292] the negative symptoms measured by the SOPS may not be directly measuring the NIMH-MATRICS five negative symptom domains, which include asociality, anhedonia, avolition, blunted affect, and alogia.[135] 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.[292] 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).[217] Next, the Scale for the Assessment of Negative Symptoms (SANS)[293] 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.[227] Another issue that arises from using the SANS to measure negative symptoms is that it does not align with the NIMH-MATRICS 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)[294] 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,[295] 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)[296] 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)[160] was the most commonly used scale followed by the Social Adjustment Scale (SAS),[297] WHOQOL-BREF social relationships,[298] Social Functioning Scale (SFS),[299] and the Social Network Index (SNI).[300] 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)[160] 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,[301] 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.[301] For anhedonia and social functioning, we performed a post-hoc sensitivity analysis and found that by dropping one study,[302] 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.

4.6.2 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,[213,303,304] future clinical trials may want to design interventions that are primarily geared towards impacting both negative symptoms and functioning.

4.6.3 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.

4.7 Supplementary Material

Supplementary Material: Searches

MEDLINE, Embase, PsychINFO, EBM database

S1: (CHR or APS or CHR# or UHR or "basic symptom*" or "ultra high risk" or "clinic* high risk" or "attenuated psych* syndrome" or prodrome* or ARMS or "at risk mental state" or "psyc* risk").mp.

S2: (negative symptom* or (expression adj1 emotion*) or "ideational richness" or "experience of emotion*").mp. or exp Motivation/cl, pd, px or asociality.mp. or anhedonia.mp. or exp Anhedonia/ or avolition.mp. or "blunted affect*".mp. or alogia.mp.

S3: Social Adjustment/ or ((function* adj2 social*) or (social* adj2 isolation) or (role* adj2 function*) or "global function*" or ((social* or clinical* or role*) and (function* or scale* or assess*)) or SOFAS or "social occupational functioning assessment scale" or SFS or "social functioning scale" or SSIS or "social skills improvement scale" or SAS-SR or "social adjustment scale: self report" or GFS or "global functioning: social" or GFR or "global functioning: role").mp.

S4: S1 AND S2 AND S3

CINAHL
S1: “CHR” OR “APS” OR “CHR-P” OR “UHR” OR “psychosis risk” OR “ultra high risk” OR “clinical high risk” OR “attenuated psychosis syndrome” OR “prodrome” OR “psychosis risk”
S2: “negative symptoms” OR “expression of emotion” OR “ideational richness” OR “experience of emotion” OR “motivation” OR “asociality OR “anhedonia” OR “avolition” OR “blunted affect” OR “alogia”
S3: (MM “Social Adjustment”) OR “social adjustment” OR (function* social*) OR (social* isolation) OR (role* function*) OR “global function*” OR ((social* or clinical* or role*) and (function* or scale* or assess*)) OR SOFAS OR “social functioning scale” OR SSIS OR “social skills improvement scale” OR SAS-SR.mp. OR “social adjustment scale: self report” OR GFS OR “global functioning: social” OR GFR.mp. OR “global functioning role”
S4: S1 AND S2 AND S3

Supplementary Table 1. Observational studies examining negative symptoms and functioning included in qualitative synthesis (k=20).

Reference + Year	Country	Study Design	Sample Size	CHR Participants		
				N	Age (*M*,SD)	Male (N, %)
1. *Carrion et al., (2017)*	USA	Longitudinal	239	138	16.0(NR)	96(70)
2. *Azis et al., (2018)*	USA	Cross-sectional	214	214	22.2(3.8)	113(53)
3. *Carrión, Demmin, Auther, McLaughlin, Olsen, Lencz, Correll, Cornblatt* [157]	USA	Longitudinal	76	76	16.0(2.2)	52(68)
4. *Carrion et al., (2013)*	USA	Longitudinal	160	92	16.0(2.2)	58(63)
5. *Cornblatt et al., (2012)*	USA + Canada	Longitudinal	100	100	18.1(NR)	64(64)
6. *Glenthoj, Jepsen, Hjorthoj, Bak, Kristensen, Wenneberg, Krakauer, Nordentoft, Fagerlund* [159]	Denmark	Cross-sectional	116	84	24.5(4.7)	35(42)
7. *Healey et al., (2018)*	USA + Canada	Cross-sectional	271	171	19.8(4.5)	98(57.4)
8. *Lin et al., (2011)*	Australia	Longitudinal	230	230	26.4(NR)	99(43)
9. *Lyngberg, Buchy, Liu, Perkins, Woods, Addington* [263]	USA + Canada	Cross-sectional	160	160	19.8(4.6)	88(55)
10. *Masillo et al., (2016)*	Italy	Cross-sectional	147	39	17.4(5.6)	21(53.8)
11. *Mechelli et al., (2017)*	Australia	Longitudinal	416	416	19.4(3.4)	200(48)
12. *Minichino et al., (2017)*	Italy	Longitudinal	138	116	24.2(NR)	60(52)
13. *Niendam, Bearden, Zinberg, Johnson, O'Brien, Cannon* [305]	USA	Longitudinal	35	35	17.3(4.3)	21(60)
14. *Quijada et al., (2012)*	Spain	Longitudinal	31	31	15.7(3.1)	23(74)
15. *Schlosser, Campellone, Biagianti, Delucchi, Gard, Fulford, Stuart, Fisher, Loewy, Vinogradov* [166]	USA	Cross-sectional	85	85	18.7(4.5)	49(58)
16. *Tarbox et al., (2013)*	USA + Canada	Cross-sectional	270	270	18(4.5)	160(59.3)
17. *Tarbox-Berry et al., (2018)*	USA + Canada	Cross-sectional	232	156	19.8(4.6)	86(55.1)
18. *Yung et al., (2019)*	Australia	Longitudinal	363	363	18.7(3.2)	175(48.2)
19. *Chang et al., (2018)*	China	Cross-sectional	110	110	20.9(6.7)	53(48.2)
20. *Chudleigh et al., (2011)*	Australia	Cross-sectional	60	20	20.75(2.7)	11(55)

Abbreviations: CHR= clinical high risk

Chapter 5: Negative Symptoms: Associations with Defeatist Beliefs, Self-Efficacy, and Maladaptive Schemas in Youth At Risk for Psychosis

5.1 Preface

Research presented as part of this chapter is currently in a manuscript being submitted as; Daniel Devoe; K.S. Cadenhead; Barbara Cornblatt, Eric Granholm, Jean Addington. Negative Symptoms: Associations with Defeatist Beliefs, Self-Efficacy, and Maladaptive Schemas in Youth At Risk for Psychosis.

Author Contributions: Drs. Addington, Cadenhead, Cornblatt, Granholm were responsible for the design of the study and for the supervisions of all aspects of data collection. Mr. Devoe was responsible for the statistical analyses. Mr. Devoe wrote the initial manuscript. Dr. Addington was involved in writing the subsequent drafts of the manuscript.

5.2 Abstract

Background: Investigations into possible mechanisms that may contribute to the development, maintenance, and exacerbation of negative symptoms are needed. Defeatist beliefs, self-efficacy, and early maladaptive schemas have been shown to contribute to negative symptoms in schizophrenia. Likewise, negative symptoms occur in those at clinical high-risk (CHR) for psychosis. The aim of this study was to determine if negative symptoms were associated with defeatist beliefs, self-efficacy, and early maladaptive schemas in CHR participants of a group therapy intervention study.

Method: All CHR participants (N=203; 99 males, 104 females) were recruited as part of a 3-site randomized control trial: Recovery through Group Study (Regroup). Negative symptoms, defeatist beliefs, self-efficacy and early maladaptive schemas were assessed by trained clinical raters. Mediation analyses were conducted to examine the relationship between defeatist beliefs, self-efficacy, functioning, and negative symptoms.

Results: The majority of CHR youth (72.9%) had at least one negative symptom of moderate to above moderate severity at baseline. CHR youth exhibited a considerable amount of defeatist performance beliefs, asocial beliefs, and poor social self-efficacy. In addition, asocial beliefs, negative self-schemas, and social self-efficacy were all significantly associated with negative symptom total scores. In multiple mediation analyses, both asocial beliefs and social self-efficacy mediated the effects of social

functioning on negative symptoms. Finally, defeatist performance attitudes significantly mediated the effects of role functioning on negative symptoms.

Conclusion: These results highlight the importance of considering beliefs and attitudes in relation to functioning and severity of negative symptoms. Psychosocial interventions may wish to target beliefs and attitudes in effort to reduce negative symptoms and improve functioning in CHR youth.

5.3 Introduction

Negative symptoms are a major contributor to poor quality of life in patients with schizophrenia.[134,135] Furthermore, severity of negative symptoms are associated with increased functional deficits in patients with psychosis,[134,135] with both negative symptoms and functional deficits emerging before the onset of psychosis.[218,219] One possible mechanism that has been proposed for both negative symptoms and functional deficits in schizophrenia are maladaptive thinking patterns such as defeatist beliefs.[146-149] Defeatist performance beliefs are defined as negative cognitions about one's capacity to successfully accomplish goal-directed behaviors.[146,306] Beck and colleagues,[306,307] proposed that both defeatist performance beliefs (e.g., "If I fail at my work, then I am a failure as a person") and asocial beliefs (e.g., "Making new friends isn't worth the energy it takes") contribute to negative symptoms and poor functioning in schizophrenia. Numerous studies support this model reporting a relationship between negative symptoms and defeatists beliefs, [147-151] with change in dysfunctional beliefs partially mediating change in negative symptoms[308] and the effect of treatment on negative symptoms being mediated by defeatist beliefs and asocial beliefs.[309] Indeed, one meta-analysis found a significant relationship between defeatist performance beliefs and both negative symptoms and functional outcomes in schizophrenia studies.[152] Similarly, self-efficacy beliefs are central to both motivation and engagement in goal-directed behaviors.[310] Self-efficacy beliefs are defined as a person's belief in their ability to perform a behavior or accomplish tasks (e.g., confidence in one's ability to ask a friend for advice). Self-efficacy beliefs are associated with negative symptoms in

patients with schizophrenia,[311-313] which in turn have been shown to influence functioning.[149]

Schema theory may also contribute to understanding negative symptoms in schizophrenia. According to Young and colleagues,[314] in schema theory the emergence of early maladaptive schemas are generated in childhood based on the amalgamation of memories, emotions, and cognitions concerning oneself and one's relationship with others.[314] Adding to this Beck and colleagues proposed that the content of schemas develop through the cognitive triad (e.g., negative beliefs about: 1) one's self, 2) external situations, and 3) the future),[315,316] which in turn may contribute to amotivation, anhedonia, and asociality.[315] Patients with schizophrenia have greater maladaptive schemas compared to healthy controls[317] and early maladaptive schemas relating to social isolation and defectiveness have been significantly associated with negative symptoms in patients with schizophrenia.[318]

Similar to schizophrenia patients, those at clinical high risk (CHR) for psychosis often have significant and severe negative symptoms.[155,156,319] With one study indicating that over 80% of those at CHR for psychosis present with at least one negative symptom of moderate severity.[223] Several studies have shown that negative symptom severity is associated with increased functional deficits in CHR youth,[126,164-167] and both have been reported to be main reasons why CHR youth seek out clinical services.[225]

To date, two studies have examined defeatist beliefs in CHR youth. The first study demonstrated that CHR youth endorsed defeatist beliefs more than healthy controls, and that defeatist beliefs were associated with severity of negative symptoms.[168] The second study found that defeatist performance beliefs did not differ

between controls and CHR, and that defeatist performance beliefs were not associated with negative symptoms.[320] In a third study a trend of higher negative-self schemas was found in a CHR sample with persistent negative symptoms versus those without.[319] For maladaptive schemas, one longitudinal study found that CHR participants had significantly more maladaptive schemas compared to healthy controls but that these maladaptive schemas had no correlation to negative symptoms.[321]

To our knowledge only two studies have examined self-efficacy in CHR samples.[322,323] The first study demonstrated that CHR youth have both significantly lower general self-efficacy and lower social self-efficacy compared to that of healthy controls.[39] Moreover, another study reported that CHR participants more frequently reported low self-efficacy compared to first episode psychosis patients.[323] However, neither study examined the relationship between self-efficacy and negative symptoms in CHR. Lastly, no studies have been conducted examining the relationship between asocial beliefs and negative symptoms in CHR.

Thus, examining negative symptoms in those at CHR sample may provide insights into their development, maintenance, and exacerbation. Determining whether negative symptoms in CHR youth are directly related to defeatist performance beliefs, asocial beliefs, maladaptive schemas, and self-efficacy may highlight possible mechanisms that contribute to them. Most mediational studies in schizophrenia utilize a path with functioning as an outcome, not driving defeatist attitudes to negative symptoms. However, during adolescences, what one achieves in their roles (i.e., social or occupational) may drive attitudes and self-efficacy which in turn may drive negative

symptoms (ie, functioning → defeatists attitudes / self-efficacy → diminished motivation).

The present study examined negative symptoms in a large sample of CHR youth. The aim of this current study was to: (1) determine the occurrence of defeatist performance beliefs, asocial beliefs, poor self-efficacy, and maladaptive schemas in a CHR sample, (2) examine the correlations between negative symptoms, defeatist performance beliefs, asocial beliefs, maladaptive schemas, and self-efficacy, and (3) explore potential mediators between the relationship of functioning (i.e., social and role) and negative symptoms and provide an estimation of mediated effects.

5.4 Method

5.4.1 Setting and participants

All CHR participants (N=203; 99 males, 104 females) were recruited as part of a 3-site (University of Calgary, Zucker-Hillside Hospital, and University of California San Diego) randomized control trial: Recovery through Group Study (ReGroup). CHR participants between the ages of 13 and 30 years old were referred by health care providers, social service agencies, educators, or were self-referred in response to community education. Prospective participants underwent a telephone screen to rule out any youth who may already be psychotic and those for whom it seemed likely that they could meet Criteria of Psychosis-risk Syndromes (COPS) were subsequently invited to an in-person eligibility evaluation and consent. CHR participants were included in the study if they met the following criteria: (1) age between 13 and 30 years old; (2) understand and sign an informed consent (or assent for minors) in English; (3) currently meet or have met in the past four years diagnostic criteria for a psychosis-risk

syndrome as per COPS criteria; (4) had at least one Scale of Psychosis-risk Symptoms (SOPS) attenuated symptom rated 3 and no symptom rated 6; (5) ratings on the Global Functioning: Social Scale or Role Scale were rated 7 or less. CHR subjects were excluded based on the following criteria: (1) meet criteria for current or lifetime Axis 1 psychotic disorder; (2) impaired intellectual functioning (IQ<70); (3) past or current history of a clinically significant central nervous system disorder that may contribute to prodromal symptoms or confound their assessment; (4) substance dependence in the past 3 months; and (5) the diagnostic psychosis-risk symptoms are or were clearly caused by an Axis 1 disorder, including substance use disorders, in the judgment of the evaluating clinician. All participants provided written informed consent, including parental consent.

5.4.2 Assessments

5.4.2.1 CHR Criteria

Participants were assessed for CHR criteria using the Criteria of Psychosis-risk Syndromes (COPS) based on the Structured Interview for Psychosis-risk Syndromes (SIPS).[36]

5.4.3.2 Negative Symptoms

Negative symptoms were rated on the SOPS negative symptom subscale based on the SIPS.[36] According to the NIMH-MATRICS negative symptom consensus the agreed upon domains of negative symptoms include avolition, asociality, anhedonia, blunted affect, and alogia.[135] Thus, in the current analysis the SOPS negative symptoms were restricted to social anhedonia (N1), avolition (N2), and expression of emotion (N3), whereas experience of emotions and self (N4), ideational richness (N5), and

occupational functioning (N6) were excluded. A total negative symptom score was calculated by adding N1, N2, and N3.

5.4.3.3 Defeatist Attitudes

To assess defeatist performance attitudes the Defeatist Performance Attitude Scale (DPAS) by Beck and colleagues was utilized. The DPAS is a 15-item self-report subscale derived from a factor analysis of the Dysfunctional Attitude Scale.[324] The DPAS rates defeatist attitudes on a 1–7 Likert scale in regards to one's ability to perform tasks. Higher total scores indicate more severe defeatist performance attitudes (range: 15-105).

To further understand aversive social beliefs as opposed to behaviours Grant and Beck developed the Asocial Beliefs Scale (ABS),[325] which is a 15-item scale (range =0-15) derived from the Revised Social Anhedonia Scale (RSAS).[326] Items are rated either true or false with higher scores representing more severe asocial beliefs.

5.4.3.4 Self-Efficacy

To assess social self-efficacy the Social Self-Efficacy subscale from the Revised Self-Efficacy Scale was utilized.[327] This subscale measures how confident individuals are in performing everyday social behaviors (i.e., "Go to a party with friends"). The Social Self-Efficacy subscale is a 19-item scale rated from 0% to 100% with higher scores reflecting greater self-efficacy.

5.4.3.5 Schemas

The Brief Core Schema Scale (BCSS) is a self-report scale utilized to assess both negative and positive schemas.[328,329] The BCSS has 24-items assessed on a 5-point rating scale regarding beliefs about the self and others. Four total scores are

obtained: negative-self, positive-self, negative-others, and positive-others. Higher scores on the negative items indicate more maladaptive schemas.

5.4.3.6 Functioning

To assess role and social functioning, the Global Functioning: Role (GF:R) and the Global Functioning: Social (GF:S) scales were used.[160,184] The GF:R measures the level of role functioning at work or school. The GF:S measures the level of social contact, friendships, age appropriate intimate relationships, and involvement with family members. The GF:R and GF:S are rated on a 10-point scale, with higher scores indicating higher functioning.

5.4.3.7 Analyses

Descriptive data for demographics were reported using mean(sd) or n(%) where applicable. Pearson *r* was utilized to examine the correlations between negative symptoms, defeatist performance beliefs, asocial beliefs, maladaptive schemas, social self-efficacy, and functioning.

Mediation analyses were conducted using the PROCESS macro for SPSS developed by Hayes,[330] a tool for conducting conditional process path analysis using ordinary least squares regression. PROCESS uses bias corrected bootstrap confidence intervals for inference about indirect effects. This allows for computation of the indirect effect (path a x path b) confidence interval of 95% and 5,000 bias corrected bootstrap samples were used for all PROCESS tests.[330,331] Therefore, the first mediation model estimated the “a path” [(GF:Role) to [DPAS or Asocial Beliefs or Social Self-efficacy or Negative Schemas], “b path” [DPAS or Asocial Beliefs or Social Self-efficacy or Negative Schemas to negative symptoms] and mediated effects (*ab*) of functioning on

negative symptoms through [DPAS or Asocial Beliefs or Social Self-efficacy or Negative Schemas] with PROCESS model 4. Next, the second mediation models estimated the “a path” [(GF:Social) to [DPAS or Asocial Beliefs or Social Self-efficacy or Negative Schemas], “b path” (DPAS or Asocial Beliefs or Social Self-efficacy or Negative Schemas to negative symptoms) and mediated effects (*ab*) of functioning on negative symptoms through (DPAS or Asocial Beliefs or Social Self-efficacy or Negative Schemas) with PROCESS model 4.

5.5 Results

5.5.1 Sample Characteristics

The mean age of CHR participants was 17.4 years (*SD*=3.9), with 99 males (49%) and 104 females (51%), see Table 5.1. CHR participants had an average of 10.4 years of education (*SD*=2.6). A total of 126 participants identified themselves as Caucasian (62%), 21 (10%) as African American, and 56 (28%) as other minority. The majority of CHR participants were currently living at home with family members (89%) and 60% had not worked within the past year. See Table 5.1.

Table 5.1 Baseline Demographics

Demographic Characteristic	***Mean (SD)***
Age in years	17.4 (3.9)
Years of education	10.4 (2.6)
	Number (%)
Sex	
Male	99 (49)
Female	104 (51)
Race	
Caucasian	126(62.1)
African American	21(10.3)
Other Minority	56(27.6)
Current living arrangement	
Living with family	180 (88.6)
Living with spouse/partner	10 (4.9)
Living on own in apartment/house	3 (1.5)
Living with others	10 (4.9)
Current employment	
Working full-time	9 (4.4)
Working part-time	30 (15.3)
Worked in past year	41 (20.2)
Not worked in past year	122 (60.1)

5.5.2 Negative Symptoms

The majority of CHR youth (72.9%) had at least one negative symptom (i.e., SOPS N1 or N2 or N3) of moderate to above moderate severity (i.e., rated ≥ 3 on the SOPS). Eighty-eight (43.4%) participants rated on one symptom in the moderate to above moderate severity range (i.e. SOPS ratings of 3 and 4), and 60 (29.5%) reported negative symptoms in the severe range (i.e. SOPS ratings of 5-6). In terms of prevalence for specific negative symptoms of ≥ 3 severity rating at baseline, avolition (N2) was the most reported negative symptom item followed by social anhedonia (N1). Expression of emotion (N3) was the least reported symptom, see Table 5.2.

5.5.3 Beliefs and Attitudes

Mean scores and standard deviations for the Defeatist Performance Attitude Scale, Asocial Beliefs Scale, Social Self-Efficacy, and the Brief Core Schema Scale are presented in Table 5.2.

Table 5.2 Clinical and Belief / Attitude Measures

Measure	***Mean (SD)***
Clinical Measures	
N1 Social Anhedonia	2.67 (1.7)
N2 Avolition	2.73 (1.7)
N3 Expression of Emotion	1.13 (1.4)
Negative Symptom Total (N1 +N2 + N3)	6.53 (3.7)
Functioning Measures	
GF:Role	5.5 (2.3)
GF:Social	5.9 (1.3)
Belief / Attitude Measures	
Defeatist Performance Beliefs	55.22 (18.9)
Asocial Beliefs	7.59 (3.4)
Social Self-Efficacy	49.1 (22.3)
Negative schemas About the Self	7.4 (6.6)
Negative schemas About the Others	7.4 (6.0)

Abbreviations: GF = Global Functioning

5.5.4 Correlations Between Scales

Correlations and p-values are reported in Table 5.3. These results suggest significant modest to strong associations between defeatist performance attitudes, asocial beliefs, social-self efficacy, negative schemas about the self, and negative schemas about others. Although some correlations were significant the *r* was weak (e.g., negative symptoms and BCSS negative-self).

Table 5.3 Correlations Between Scales

	Negative Symptom Total	Asocial Beliefs	BCSS Negative-Self	BCSS Negative-Others	Defeatist Performance Attitudes	Social Self-Efficacy	GF:Role	GF:Social
Negative Symptom Total	-							
Asocial Beliefs	.289**	-						
BCSS Negative-Self	.182*	.402**	-					
BCSS Other-Negative	-.045	.351**	.460**	-				
Defeatist Performance Attitudes	.088	.386**	.636**	.341**	-			
Social Self-Efficacy	-.258**	-.594**	-.421**	-.243**	-.436**	-		
GF:Role	-.310**	.034	.038	.011	.175*	-.044	-	
GF:Social	-.573**	-.172*	.017	.106	-.031	.231**	.154*	-

** Correlation is significant at the 0.01 level, * Correlation is significant at the 0.05 level.

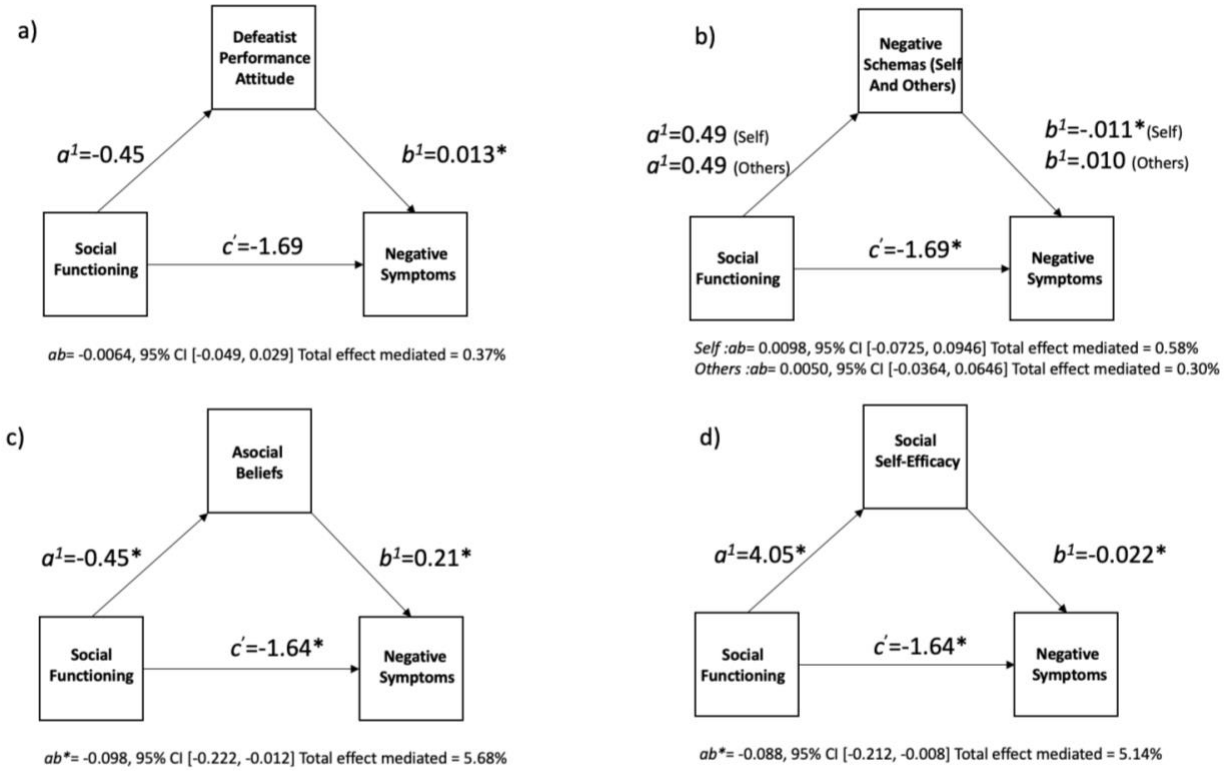
Abbreviations: BCSS = Brief Core Schema Scale; GF = Global Functioning

5.5.5 Mediation Analyses

Functioning on Mediators

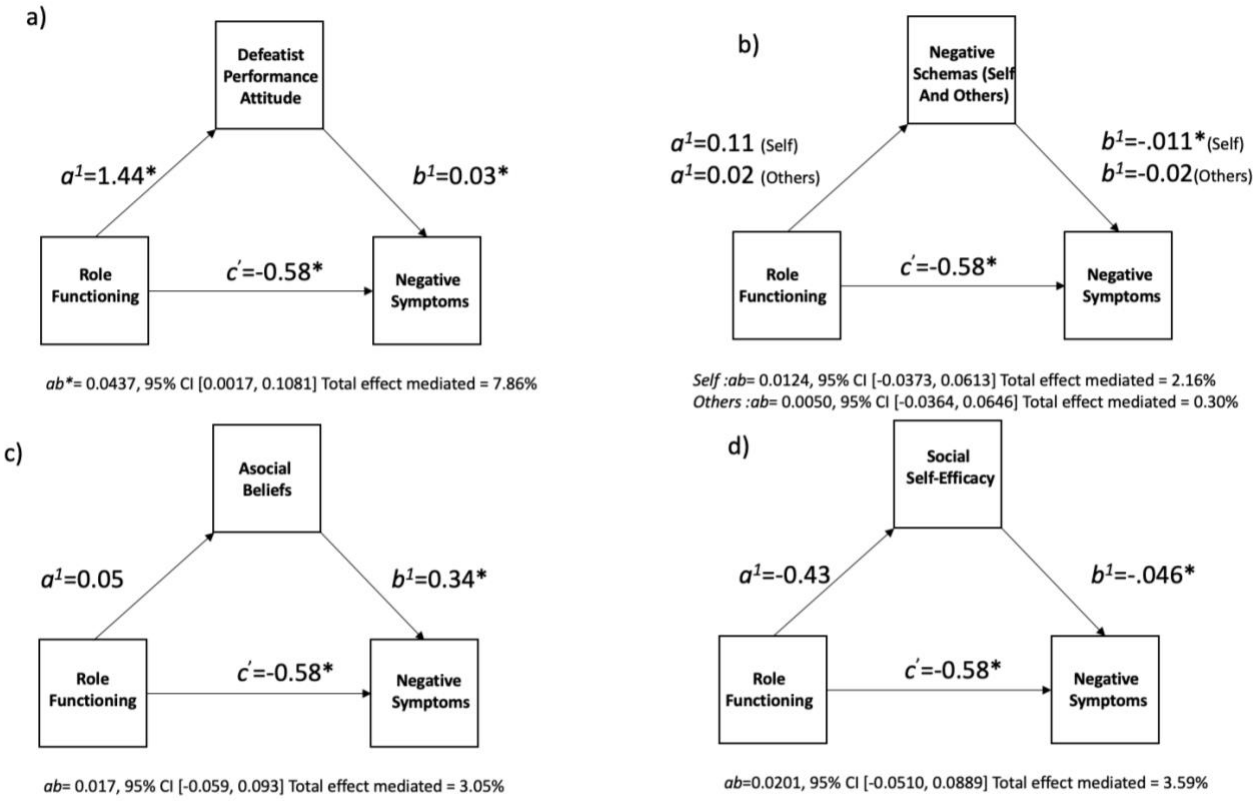
Results of models estimating the "*a* path" [functioning (social or role) to mediator], "*b* path" (mediator to outcome) and mediated effects (*ab*) of functioning on negative symptoms through dysfunctional attitudes (DPAS, ABS) or social self-efficacy or negative schemas are shown in Figures 5.1 and 5.2. The "*a* path" analyses examined the effect of functioning (social or role) on the baseline mediator variable.

Figure 5.1



Results of models estimating the mediation effects of social functioning on negative symptoms through asocial beliefs or defeatist performance attitudes or social self-efficacy.
*$P < .05$

Figure 5.2



Results of models estimating the mediation effects of role functioning on negative symptoms through asocial beliefs or defeatist performance attitudes or social self-efficacy.
*P < .05

Mediator Relations with Outcome Variables

The "*b* path" analyses, which examined associations between asocial beliefs, defeatist performance attitudes, negative schemas, or social self-efficacy as mediators on outcomes of negative symptoms, revealed several statistically significant associations. More severe asocial beliefs were associated with greater negative symptoms. More severe defeatist performance attitudes were associated with greater negative symptoms. Finally, social self-efficacy and negative schemas about the self were associated with greater negative symptoms whereas negative schemas about others were not.

Estimation of Mediated Effects

Mediation effects (*ab*) and associated 95% CIs were directly estimated. Specifically, both asocial beliefs and social self-efficacy mediated the effects of social functioning on negative symptoms (*ab* = −0.098, *P* < .05 and *ab* = -0.088, *P* < .05) whereas defeatist performance attitudes and negative schemas did not significantly mediate this relationship. Finally, defeatist performance attitudes significantly mediated the effects of role functioning on negative symptoms (*ab* = 0.04, *P* < .05) whereas asocial beliefs, social self-efficacy, and negative schemas did not significantly mediate this relationship.

5.6 Discussion

To our knowledge this is the first study to utilize the defeatist performance attitude scale, asocial beliefs scale, and social self-efficacy scale in a CHR sample. Several schizophrenia studies have utilized the defeatist performance attitudes scale, all of which reported means in the 43-52 range.[306,332-334] Comparatively, this suggests that

defeatist performance attitudes appear to be more severe in CHR youth (M=55.2) compared to patients with schizophrenia and healthy controls who typically score in the low 30s.[306,333,334] Likewise, schizophrenia studies have also utilized the asocial beliefs scale,[309,325] both of which reported means below that of the current CHR youth which indicates that asocial beliefs appear to be more severe in CHR youth as well. In terms of social self-efficacy, CHR youth in this study had poorer social self-efficacy (M=49.1) compared to patients with schizophrenia (range 71-74).[327] Finally, for negative schemas about the self and others, CHR youth in this study had comparable scores to previously published scores in CHR individuals and those with psychosis.[321] Thus, a concerning discovery of this study is that defeatist performance attitudes, asocial beliefs, and poor social self-efficacy add to the difficulties that CHR youth already endure and possibly more so than those with schizophrenia. However, the correlations between the beliefs and attitudes scales were all significant, suggesting they may be measuring similar or at least overlapping concepts. One possible explanation for the higher scores in CHR youth compared to schizophrenia for defeatist attitudes is that CHR youth potentially have greater insight, however one study has suggested that those at CHR do not have greater insight than those with schizophrenia.[335]

Surprisingly , defeatist performance attitudes were not associated with negative symptoms, which although supported by one CHR study,[320] is contradictory to both an earlier CHR study,[168] and a meta-analysis in schizophrenia research which reported a small yet significant effect-size between negative symptoms and defeatist performance attitudes.[152] One possible explanation is that the relationship may not be linear as a previous study in schizophrenia demonstrated that only those in the high DPAS tertile

had high negative symptoms.[336] As in previous studies with schizophrenia patients, asocial beliefs and social self-efficacy were significantly associated with negative symptoms.[309,311-313,325] Finally, for negative schemas about the self and others, negative symptoms were not significantly related to negative schemas about others and had a very low significant correlation with negative schemas about the self. This is corroborated by a larger CHR study that showed that negative schemas appear to have no correlation to negative symptoms.[321] However, negative schemas are more prominent in CHR youth with persistent negative symptoms,[319] and perhaps the lack of association in the current results are due to using only the baseline assessment of negative symptoms, which may attenuate or increase in other CHR individuals over time.

For the mediation analyses, the overall goal was to better understand the pathway between both social and role functioning and negative symptoms by exploring how beliefs and attitudes might mediate these relationships. First, defeatist performance attitudes mediated the relationship between role functioning and negative symptoms, meaning that those with reduced functioning also reported greater defeatist performance attitudes and in turn this led to increased negative symptoms. Another interpretation is that lower levels of defeatist performance beliefs contribute to better role functioning, which in turn lead to a reduction in negative symptoms. These results are consistent with studies using structural equation modeling in schizophrenia which have found a direct path from defeatist performance beliefs to negative symptoms and from negative symptoms to functional outcome.[332,337,338] Next, both asocial beliefs and social self-efficacy significantly mediated the effects social functioning on negative

symptoms, meaning that those with reduced social functioning also reported greater asocial beliefs or less social self-efficacy and in turn this lead to increased negative symptoms. This is supported by a previous model that demonstrated that asocial beliefs accounted for 18% of the variability in social functioning in patients with schizophrenia[325] and predicted asocial behavior one year later in patients with schizophrenia.[325] These results are also consistent with the model proposed by Beck and colleagues,[306,307] that defeatist attitudes contribute to negative symptoms and poor functioning and that self-efficacy beliefs are central to both motivation and engagement in goal-directed behaviors.[310] Perhaps not surprisingly only defeatist performance attitudes (i.e., If I fail at my work, then I am a failure as a person) mediated the relationship with role functioning which contains items directly to role functioning whereas asocial beliefs (i.e., taps beliefs related to social isolation) and social self-efficacy (i.e., measures ones confidence to perform a social behavior) only mediated the relationship with social functioning both of which measure some element closely related to social functioning. Negative schemas did not mediate the relationship in either model which may be due their broad nature (i.e., I am bad), which may not necessarily correspond to specific functional deficits (i.e., social or role functioning). Most schizophrenia studies utilize a path with functioning as an outcome, not driving attitudes to negative symptoms. However, this study represents a novel way of looking at this path in that during adolescences, what one achieves in their roles may drive their attitudes and self-efficacy which in turn may drive both their negative symptoms and role functioning up or down, in a cyclical fashion. Our results have important implications for the understanding the relationship between functioning, beliefs and

attitudes, and negative in that this relationship appears in much younger individuals than previous studies have reported and prior to the onset of schizophrenia. Adding to this, beliefs and attitudes appear to be much more severe in CHR youth. Thus, in this instance our findings suggest that in those at CHR for psychosis negative beliefs regarding positive outcomes may contribute to poorer functioning (e.g., school performance; hanging out with friends), which reduces motivation and the ability to feel pleasure in these events. This may represent a window of opportunity for early psychosocial interventions to target negative symptoms before they stabilize by challenging these negative belief patterns earlier in their course. These results also have implications for assessment in that currently beliefs and attitudes are not widely assessed in CHR youth clinical services.

5.6.1 Limitations

This study had the unique opportunity to explore negative symptoms and their relationship with beliefs and attitudes in a large CHR sample. However, some limitations should be considered when interpreting the current study results. First, the inclusion criteria for this study required that ratings on the GF:S or the GF:R were rated 7 or less, meaning that CHR youth with potentially better functioning were eliminated. Thus, restricting the sample to those with poorer functioning could have overestimated or underestimated ratings on beliefs, attitudes, and negative symptoms scales in CHR youth in this study. However, the mean ratings of the of the GF:S and GF:R in the current study appear to be similar to previous studies in CHR. [160,164]

A second limitation was that we utilized the SOPS negative symptom subscale to measure negative symptoms, which does not measure the five recommended NIMH-

MATRICS negative symptom domains: asociality, anhedonia, avolition, blunted affect, and alogia.[135] Thus, only four areas of negative symptoms were measured including social anhedonia (i.e., asociality and anhedonia), avolition, and expression of emotion, with no measure of alogia used. However, we eliminated SOPS negative symptoms of emotions and self (N4), ideational richness (N5), and occupational functioning (N6) in attempt to align the negative symptoms in this study with the recommended NIMH-MATRICS negative symptom domains. In a similar vein, it is possible that by reducing negative symptoms to three items that the negative symptoms were not severe enough and consequently this impacted the association between negative symptoms and defeatist performance beliefs seen in schizophrenia samples.

A third limitation to this study is that there is no control group. In addition, since there is no other CHR study that has utilized the defeatist performance attitudes scale, asocial beliefs scale, and the social-self efficacy subscale the current results are difficult to compare other CHR studies.

Finally, another limitation is that the current study only examined negative symptoms and beliefs at baseline. Thus, it is possible that both negative symptoms and beliefs may attenuate or exacerbate over longer periods of time making it important to examine this relationship in longitudinal studies and those with persistent negative symptoms.

5.6.2 Directions for Future Research

The results of the current study may lead to some possibilities for future research. First, future studies may wish to employ a measurement of negative symptoms that aligns with consensus to further improve our understanding of the relationship between beliefs, functioning, and negative symptoms in CHR. Second,

longitudinal studies are needed to examine the course of attitudes and beliefs in CHR youth and how they relate to functioning and negative symptoms over time. Third, targeting beliefs and attitudes may help improve functioning and negative symptoms in CHR youth. Thus, future trials may wish to design interventions that target attitudes and beliefs.

5.6.3 Conclusion

Negative symptoms are common in individuals at CHR for psychosis and beliefs and attitudes play an important role between the relationship between poor functioning and severity of negative symptoms. Thus, psychosocial interventions may wish to target beliefs and attitudes in effort to reduce negative symptoms in CHR youth.

Chapter 6: Conclusion Chapter

The overall goal of this thesis was to investigate possible mechanisms that may contribute to the development, maintenance, and exacerbation of negative symptoms in youth at clinical high risk (CHR) for psychosis as well as potential treatments. The first paper was a systematic review and both pairwise and network meta-analysis designed to examine the current state of the literature for treatment of negative symptoms in CHR. Although the search results revealed 32 treatment studies that met the inclusion criteria no treatments significantly reduced negative symptoms in CHR youth in both the network meta-analysis and the pairwise meta-analysis. In this systematic review and meta-analysis most treatment trials were design to target transition to psychosis and versus targeting negative symptoms, which may have limited the impact of the reviewed treatments on negative symptoms.

The second paper examined persistent negative symptoms (PNS) longitudinally in a large CHR for psychosis sample. In this paper the sample was divided into two groups, a persistent negative symptom group versus those without persistent negative symptoms. Those with PNS had significantly poorer social and role functioning compared to those without PNS at multiple time-points. Next, a trend emerged demonstrating higher negative-self schemas in the persistent negative symptom group; however, this result was lost when controlling for persistent depressive symptoms. Finally, there were no significant differences between the groups on neurocognition, social cognition, and transition to psychosis.

The third paper was a systematic review and meta-analysis designed to summarize the relationship between negative symptoms and functioning in CHR samples. The systematic search results revealed 41 studies that examined this

relationship in CHR studies. In the meta-analysis, negative symptom total scores were significantly associated with poorer global functioning, social functioning, and role functioning. When examining negative symptom domains; avolition, anhedonia, and blunted affect were each significantly and independently associated with poorer social functioning and role functioning.

The fourth and final paper examined if negative symptoms were first associated with defeatist beliefs, self-efficacy, and early maladaptive schemas in a CHR sample and if these beliefs and attitudes mediated the pathway between functioning to negative symptoms (i.e., functioning → beliefs / attitudes → negative symptoms). In this paper negative symptoms were significantly associated with asocial beliefs, negative-self schemas, and social self-efficacy. The mediation analyses revealed that both asocial beliefs and social self-efficacy mediated the effects of social functioning on negative symptoms whereas defeatist performance attitudes significantly mediated the effects of role functioning on negative symptoms.

When considering the results of each paper outlined above it is also important to consider the limitations that come with each of the papers. For the first paper, which examined treatment and negative symptoms, the major limitation was that most studies did not design treatments to address negative symptoms nor were the samples chosen for having negative symptoms. In fact, only one study in the treatment meta-analysis utilized negative symptoms as a primary outcome.

For the second paper, which examined persistent negative symptoms, only a few CHR youth had PNS (i.e., 9%) which was further reduced after excluding those with persistent depressive symptoms (i.e., 4%). This low PNS rate in CHR youth is much

lower than that of PNS in first episode psychosis[138] and thus some may consider PNS not to constitute a major issue in CHR youth. Adding to this, another limitation in this paper was utilizing the 12-month PNS criteria to determine prevalence, which is not commonly done in first episode psychosis studies. Thus, we also utilized a less restrictive criteria of 6-months to determine PNS and the prevalence estimates of PNS in CHR doubled (19%) which is more akin to the prevalence found in first episode psychosis studies.[138] A final limitation was that the PNS group had significantly more males for which the current study did not adjust for.

For the third paper, a major limitation was that the majority of studies included in the review were cross-sectional in nature making the results difficult to interpret in that it is often challenging to know whether the exposure or outcome came first. Next, there was a significant amount of high heterogeneity between studies and many studies could not be included in the meta-analysis due to study design which led to insufficient data. Lastly, papers included in the meta-analysis utilized many different functioning scales for which only a few were designed to measure functioning in CHR youth.

For the fourth paper, one important limitation to consider is the direction of mediation is attitudes and beliefs mediating the pathway between functioning to negative symptoms. Typically, in the schizophrenia literature, the pathway being explored is negative symptoms mediating the pathway between attitudes and beliefs to functioning as an outcome. However, the focus of the current thesis and paper was to examine negative symptoms as an outcome. Additionally, it is unknown as the order of these outcomes, that is whether negative symptoms, a decline in functioning, or poor attitudes and beliefs appear first in CHR youth, and whether or not this is a cyclical

relationship. Another limitation to this study is that it may not be generalizable to other CHR samples in that the sample consisted of baseline data from a large randomized control trial (RCT) where the inclusion criteria included those with poorer functioning, those who currently met criteria for CHR and those who met CHR criteria over the previous 4 years, and only participants who were willing to consent to participate in the RCT. A final limitation to this study is that there is no control group and that beliefs and attitudes were only examined at baseline.

The abovementioned limitations lead to some important limitations in CHR with respect to negative symptoms. One recurrent limitation across all four papers was the use of negative symptom scales that did not directly measure the NIMH-MATRICS five negative symptom domains, which include asociality, anhedonia, avolition, blunted affect, and alogia. This may have underestimated or overestimated the prevalence of negative symptoms, impacted the measurement of treatment on negative symptoms, and altered any associations with negative symptoms. Next, there is a lack of an agreed upon definition for PNS in CHR youth. The studies to date lack continuity in terms of a timeframe (i.e., 6-months, 12-months), what symptoms to control for in terms of sources of secondary negative symptoms (i.e., positive symptoms/extrapyramidal symptoms/depressive symptoms), and what cut-off values should be imposed when controlling for sources of secondary negative symptoms.

From this collection of papers several important observations have been made that may help shape our knowledge of negative symptoms in CHR. First, there is no effective treatment for negative symptoms in CHR and most trials have not focused on treatments that will alleviate negative symptoms. Second, negative symptoms at

moderate severity occur in the majority of CHR youth upon initial presentation, with some of these youth eventually developing PNS at similar rates of first episode psychosis patients depending on what definition is used. Those who do develop PNS have significantly worse functional outcomes but do not appear to have a higher risk of transition to psychosis compared to those without PNS. Moreover, the prevailing literature suggest that poor social and role functioning is strongly associated with negative symptoms in CHR and that this association appears to be equally strong in CHR. Next, few studies have examined the occurrence of attitudes/beliefs in CHR and the associations they may have with negative symptoms and functioning. Both beliefs and self-confidence related to socializing (i.e., asocial belief and social self-efficacy) are related to negative symptoms in CHR and appear to mediate the pathway between social functioning to negative symptoms. Defeatist performance attitudes do not appear to be related to negative symptoms in CHR, yet they mediated the relationship between role functioning to negative symptoms. Moreover, asocial belief, social self-efficacy, and defeatist performance attitudes appear to occur at higher rates in CHR when compared to patients with schizophrenia.

Thus, the four papers presented in this thesis may be important in that the current focus of identification of CHR youth is on attenuated psychotic symptoms and little attention in the detection phase is placed on negative symptoms despite the fact that most of these young people appear to have negative symptoms initially with some developing persistent negative symptoms. 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. In a similar vein, the

focus of treatment studies to date has primarily been transition to a psychotic disorder with little to no focus on negative symptoms and functioning. It is possible that identifying potential targets such as defeatist beliefs and attitudes that may be modifiable by psychosocial treatments may help alleviate both poor functioning and negative symptoms in CHR.

These papers provide clear avenues for future research. First, a newly published negative symptom scale (i.e., NSI-PR) by Strauss and colleagues that covers all the negative symptom domains needs further research to test its validity in other samples[217] and researchers may also want to consider the development of a self-report scale as well that aligns with the consensus on negative symptoms. Next, with no treatments for negative symptoms in CHR there is a strong need for future randomized control trials that can identify potential treatments to ameliorate negative symptoms. Most importantly, since not all CHR youth present with negative symptoms it is vital that future trials select for CHR youth that actual present with negative symptoms and to possibly also consider targeting those with persistent negative symptoms. In addition, a consistent definition is required in the field of CHR in order to determine what constitutes persistent negative symptoms. Potential targets for psychosocial interventions presented in this thesis that may impact negative symptoms could include asocial beliefs, social self-efficacy, and defeatist performance attitudes.

In conclusion, with no treatments established to help negative symptoms and given their significant relationship with functional impairments, an unfortunate trajectory emerges for CHR youth with negative symptoms in that they may develop persistent negative symptoms and thus require treatments that may alleviate their symptoms and

improve their day to day lives. Therefore, psychosocial interventions may wish to target defeatist attitudes and beliefs in effort to reduce negative symptoms in those at CHR for psychosis.

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Appendix A

Schizophrenia Bulletin vol. 44 no. 2 pp. 463, 2018
doi:10.1093/schbul/sbx193

ERRATUM

Erratum to: Devoe DJ, Peterson A, Addington J. Negative Symptom Interventions in Youth at Risk of Psychosis: A Systematic Review and Network Meta-Analysis. Schizophr Bull. doi:10.1093/schbul/sbx139

The authors regret that, although the text is clear that neither efficacy nor effectiveness was statistically confirmed for any of the examined treatments, the abstract and text contained a mis-statement regarding effectiveness when rank ordering treatments according to the network analysis.

Page 1: In the **Abstract under Results**, Add "The null hypothesis was not rejected for any of the 11 treatments" between the first sentence "Of 3,027…. participants." and the second sentence "Only N-methyl-D-aspartate-receptor (NMDAR) modulators trended towards a significant reduction in negative symptoms compared to placebo (SMD,-0.54, 95%CI, -1.09 to 0.02; $I^2 = 0\%$, P = 0.06)."

Page 1: In the **Conclusion of the Abstract** current wording should be deleted and the conclusions should now read: "Efficacy and effectiveness were not confirmed for any negative symptom treatment. Many studies had small samples and the majority were not designed to target negative symptoms."

Page 9, line 18/19: Delete "…demonstrated small to large effect sizes for negative symptom reduction compared to …." and replace with: "…ranked ahead of….".

Page 9: Delete the last sentence of the NMDAR Modulators section line 33 and replace with: "Lastly, SUCRA plots of the absolute effects and rank test among the 11 treatments indicated that NMDAR modulators ranked higher than the other 10 treatments, but this is in the context of no statistically supported efficacy compared to placebo."

Page 13: In the **Conclusions** of the main text the first sentence should be deleted and replaced with the following: "In conclusion, this review contained information on clinical trials of 11 treatment approaches. Support for efficacy or effectiveness did not reach statistical significance for any of the treatments. Many of the relevant studies had small samples…".

Appendix B

UNIVERSITY of York
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Systematic review

* Review title.
Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.
Negative symptom treatments in youth at risk of psychosis: a systematic review and network meta-analysis

Original language title.
For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

* Anticipated or actual start date.
Give the date when the systematic review commenced, or is expected to commence. 20/10/2016
* Anticipated completion date.
Give the date by which the review is expected to be completed. 31/01/2017
* Stage of review at time of this submission.
Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.
Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.
This field should be updated when any amendments are made to a published record and on completion and publication of the review. If this field was pre-populated from the initial screening questions then you are not able to edit it until the record is published.

The review has not yet started: Yes

Review stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	No	No

Formal screening of search results against eligibility criteria No No
Data extraction No No
Risk of bias (quality) assessment No No
Data analysis No No
Provide any other relevant information about the stage of the review here (e.g. Funded proposal, protocol not yet finalised).

* Named contact.
The named contact acts as the guarantor for the accuracy of the information presented in the register record. Daniel Devoe

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

* Named contact email.
Give the electronic mail address of the named contact. djadevoe@ucalgary.ca
Named contact address
Give the full postal address for the named contact. 82 Rosewood Road NW, T2K1N1, Canada, Alberta
Named contact phone number.
Give the telephone number for the named contact, including international dialling code. 4038005791
* Organisational affiliation of the review.
Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.
The University of Calgary

Organisation web address:
http://www.ucalgary.ca/

* Review team members and their organisational affiliations.
Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country are now mandatory fields for each person.**
Mr Daniel Devoe. University of Calgary Dr Jean Addington. University of Calgary Mr Aaron Peterson. University of Calgary

* Funding sources/sponsors.
Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Include any unique identification numbers assigned to the review by the individuals or bodies listed.
None, this is a component of my PhD thesis project

Grant number(s)

* Conflicts of interest.
List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.
None

Collaborators.
Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country are now mandatory fields for each person.**

* Review question.
State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.
Amongst youth at clinical high risk of psychosis, do treatment of negative symptoms, compared to controls decrease negative symptoms?
* Searches.
State the sources that will be searched. Give the search dates, and any restrictions (e.g. language or publication period). Do NOT enter the full search strategy (it may be provided as a link or attachment.)
A comprehensive search of MEDLINE (1946 to 2016 October 31), EMBASE (1974 to 2013 November 08),
CINAHL (1937 to October 31, 2016), EBMR (2005 to October 2016), and PyscINFO (2005 to October 2016) will be conducted.
In addition, abstracts from the annual meeting of the International Conference on Schizophrenia Research between 2012 and 2016 will be reviewed and the reference lists of included articles will be hand-searched for relevant citations. Each reviewer (D.D. and A.P) will independently perform title and abstract screening. We will include both experimental and observational studies.
Cross-sectional studies, case reports, review articles, and editorials without original data will be excluded. Disagreements will be resolved by a third party (D.P.).

There will be no restrictions on language.

Additional search strategy details can be found in the attached PDF document.

URL to search strategy.
Give a link to a published pdf/word document detailing either the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies), or upload your search strategy.Do NOT provide links to your search results.

http://www.crd.york.ac.uk/PROSPEROFILES/49319_STRATEGY_20160912.pdf
Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Yes I give permission for this file to be made publicly available

* Condition or domain being studied.
Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.
Youth at clinical high risk of psychosis is a stage prior to the development a psychosis disorder (e.g. schizophrenia). This is when you experience milder symptoms compared to schizophrenia. Negative symptoms may be an indicator for later conversion to psychosis. This study is looking at negative symptoms treatments in youth at clinical high risk of psychosis.
* Participants/population.
Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.
Inclusion: Studies that include adolescent individuals (12-35 years) with symptoms causing them to be at high risk of psychosis (as diagnosed using any recognised diagnostic criteria, e.g. SIPS, BS, CARRMS).

Exclusion: Paediatric and adults (35) studies will be excluded.

* Intervention(s), exposure(s).
Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.
RCTs involving youth at clinical high risk of psychosis containing information about negative symptoms will be included if they have reported relevant outcomes (treatment of negative symptoms) and have incorporated a standard a control group. Observational studies will be included if they report any treatment of negative symptoms.
* Comparator(s)/control.
Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.
Studies involving youth at clinical high risk of psychosis containing information about negative symptoms will be included if they have reported relevant outcomes (treatment of negative symptom prevalence) and have incorporated a standard control group.
* Types of study to be included.
Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.
We will include both experimental and observational studies. Cross-sectional studies, case reports, review articles, longitudinal data and editorials without original data will be excluded.
Context.
Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.
Studies looking at youths at clinical high risk of psychosis in any setting or country that have reported treatment of negative symptoms.

* Main outcome(s).
Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.
Treatment of negative symptoms in patients at risk of psychosis. In other words, whether or not an individual with clinical high risk symptoms, regardless of symptom severity, receives treatment of negative symptoms or a treatment reports negative symptom outcomes. This will be expressed as an standard mean difference (SMD) that represents the pooled negative symptom scores at follow-up or change scores. A network meta- analysis will be used to compare treatments in RCTs.

* Measures of effect
Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

* Additional outcome(s).
List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state ‘None’ or ‘Not applicable’ as appropriate
to the review
To estimate the reduction of negative symptoms in youth at clinical high risk of psychosis in observational studies. This will capture the rate at which an individual at clinical high risk of psychosis has a reduction in negative symptoms due to treatment.

* Measures of effect
Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

* Data extraction (selection and coding).
Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.
All data will be extracted in duplicate and will include study characteristics (country, year, study design, sample size, and duration of study), individual characteristics (age, sex, mean negative and positive symptom rates), and specific features of the individual negative symptoms (avolition, decreased expression of emotion, decreased experience of emotion and self, decreased ideational richness, deterioration in role functioning, and social anhedonia). Two reviewers (D.D. and A.P.) will independently assess the full texts of each potentially relevant study for inclusion using predetermined eligibility criteria. Disagreements will be resolved by a third party (J.A. or D.P.).
* Risk of bias (quality) assessment.
Describe the method of assessing risk of bias or quality assessment. State which characteristics of the studies will be assessed and any formal risk of bias tools that will be used.
A risk of bias assessment tool based on the Ottawa-Newcastle criteria will be applied to observational studies. For randomized studies, we will evaluate risk of bias using the

criteria adapted from Higgins et al. Quality assessment will not influence the decision to include studies.
* Strategy for data synthesis.
Provide details of the planned synthesis including a rationale for the methods selected. This **must not be generic text** but should be **specific to your review** and describe how the proposed analysis will be applied to your data.
Characteristics of the included studies will be compiled in tabular form, according to the outcomes of interest. The principal summary measures to be used will be standard mean difference (SMD). SMD will be used to compare negative symptom outcomes in individuals who receive treatment relative to the SMD in those who do not receive treatment (follow-up means or mean change scores). Data will be analyzed using Stata, version 13.1 (Stata Corp) and SPSS. Due to expected differences between studies resulting from study design, patient population, and the different rating strategies, we will combine the results using the random effects model by DerSimonian and Laird. Statistical heterogeneity will be quantified using the I- squared statistic. Publication bias will be assessed using funnel plots and Begg's test.
* Analysis of subgroups or subsets.
State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.
A stratified analyses and meta-regression will be used to examine whether the association between conversion and negative symptoms was modified by the following a priori defined variables: geographical region in which the study was conducted (European, Asian, and North American studies), severity of negative symptoms (only 3 negative symptom ratings vs all negative symptom-experiencing patients), and whether the study has reported negative symptoms alone, or negative symptoms and positive symptoms, disorganized symptoms, or general symptoms combined.

* Type and method of review.
Select the type of review and the review method from the lists below. Select the health area(s) of interest for your review.
Type of review Cost effectiveness No
Diagnostic No
Epidemiologic Yes
Individual patient data (IPD) meta-analysis No
Intervention No
Meta-analysis Yes
Methodology No
Narrative synthesis No
Network meta-analysis Yes
Pre-clinical No
Prevention No
Prognostic No
Prospective meta-analysis (PMA) No
Review of reviews No
Service delivery No

Synthesis of qualitative studies No
Systematic review Yes
Other No

Health area of the review Alcohol/substance misuse/abuse No
Blood and immune system
No
Cancer
No
Cardiovascular No
Care of the elderly No
Child health No
Complementary therapies No
Crime and justice No
Dental No
Digestive system No
Ear, nose and throat No
Education No
Endocrine and metabolic disorders No
Eye disorders No
General interest No
Genetics No
Health inequalities/health equity No
Infections and infestations No
International development No
Mental health and behavioural conditions No
Musculoskeletal No
Neurological No
Nursing No
Obstetrics and gynaecology No
Oral health No
Palliative care No
Perioperative care No
Physiotherapy No
Pregnancy and childbirth No
Public health (including social determinants of health) No
Rehabilitation No
Respiratory disorders No
Service delivery No
Skin disorders No
Social care No
Surgery No
Tropical Medicine No
Urological No
Wounds, injuries and accidents No

Violence and abuse No
Language.
Select each language individually to add it to the list below, use the bin icon to remove any added in error. English
There is an English language summary.

* Country.
Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.
Canada

Other registration details.
Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

Reference and/or URL for published protocol.
Give the citation and link for the published protocol, if there is one Give the link to the published protocol.
Alternatively, upload your published protocol to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Yes I give permission for this file to be made publicly available
Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

Dissemination plans.
Give brief details of plans for communicating essential messages from the review to the appropriate audiences.
This systematic review will be published in a psychiatric journals and conference presentations for clinicians.

Do you intend to publish the review on completion?
Yes

Keywords.
Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords will help users find the review in the Register (the words do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.
psychosis clinical high risk
negative symptoms youth

Details of any existing review of the same topic by the same authors.
Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

* Current review status.
Review status should be updated when the review is completed and when it is published. For newregistrations the review must be Ongoing.
Please provide anticipated publication date Review_Ongoing
Any additional information.
Provide any other information the review team feel is relevant to the registration of the review.

Details of final report/publication(s).
This field should be left empty until details of the completed review are available. Give the link to the published review.

Appendix C

UNIVERSITY of York
Centre for Reviews and Dissemination

Systematic review

* Review title.
Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.
Negative Symptoms and Functioning in Youth At Clinical High Risk for Psychosis: A Systematic Review and Meta-analysis

Original language title.
For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

* Anticipated or actual start date.
Give the date when the systematic review commenced, or is expected to commence. 01/06/2019

* Anticipated completion date.
Give the date by which the review is expected to be completed. 30/06/2020

* Stage of review at time of this submission.
Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.
Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.
This field should be updated when any amendments are made to a published record and on completion and publication of the review. If this field was pre-populated from the initial screening questions then you are not able to edit it until the record is published.

The review has not yet started: No

Review stage	Started	Completed	
Preliminary searches		Yes	No
Piloting of the study selection process	Yes	No	
Formal screening of search results against eligibility criteria	Yes	No	
Data extraction	No	No	
Risk of bias (quality) assessment	No	No	
Data analysis		No	No

Provide any other relevant information about the stage of the review here (e.g. Funded proposal, protocol not yet finalised).

* Named contact.

The named contact acts as the guarantor for the accuracy of the information presented in the register record. Daniel Devoe

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:
Mr Devoe

* Named contact email.
Give the electronic mail address of the named contact. djadevoe@ucalgary.ca
Named contact address
Give the full postal address for the named contact. 82 Rosewood Rd NW, Calgary, AB, T2K1N1
Named contact phone number.
Give the telephone number for the named contact, including international dialling code. 4038194157
* Organisational affiliation of the review.
Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.
University of Calgary

Organisation web address:

* Review team members and their organisational affiliations.
Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.
NOTE: email and country are now mandatory fields for each person.
Mr Daniel Devoe. University of Calgary Dr. Jean Addington. University of Calgary Ms. Amy Braun. University of Calgary
Dr. Tom Seredynski. University of Calgary

* Funding sources/sponsors.
Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Include any unique identification numbers assigned to the review by the individuals or bodies listed.
Alberta Innovates Rewarded to Dan Devoe

Grant number(s)

* Conflicts of interest.
List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.
None

Collaborators.
Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country are now mandatory fields for each person.**

* Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.
What is the direction and size of effect between negative symptoms and functioning in clinical high risk for psychosis populations?

* Searches.
State the sources that will be searched. Give the search dates, and any restrictions (e.g. language or publication period). Do NOT enter the full search strategy (it may be provided as a link or attachment.)

Database: CINAHL June 18th 2019
Database: Ovid MEDLINE June 21st 2019
Database: Embase June 21st 2019
Database: PsycINFO June 21st 2019
EBM
June 21st 2019

No Restrictions.

URL to search strategy.
Give a link to a published pdf/word document detailing either the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies), or upload your search strategy.Do NOT provide links to your search results.

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

CINAHL SEARCH EXAMPLE
S1: “CHR” OR “APS” OR “CHR-P” OR “UHR” OR “basic symptoms” OR “ultra high risk” OR “clinical
high risk” OR “attenuated psychosis syndrome” OR “prodrome” OR “prodromal” OR “ARMS” OR “At Risk Mental State” OR “psychosis risk” OR “psychotic risk”
S2: “Negative symptoms” OR “expression of emotion” OR “ideational richness” OR “experience of emotion” OR “motivation” OR “asociality” OR “anhedonia” OR “avolition” OR “blunted affect” OR “alogia”

S3: "Functioning" OR "global functioning" OR "social functioning" OR "role functioning OR "Social and Occupational Functioning Assessment Scale" OR "SOFAS" OR "GF:S" OR "GF:R" or "GAF"
Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.
Yes I give permission for this file to be made publicly available

* Condition or domain being studied.
Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.
Clinical high risk for psychosis is a stage prior to the onset of a psychotic disorder, for example schizophrenia. This condition is marked by milder psychotic symptoms as compared to schizophrenia.
Negative symptoms are related to conversion to a psychotic disorder and are currently a target of interest for treatment approaches. Understanding the links between functioning and negative symptoms may inform treatment approaches.

* Participants/population.
Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria. CHR for psychosis individuals as diagnosed by any validated scale. (e.g SIPS, CAARMS).

* Intervention(s), exposure(s).
Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.
CHR for psychosis individuals have undergone assessment of negative symptoms and functioning as
measured by various validated scales (e.g SIPS negative sub-scale, GAF, GF:S, GF:R, SOFAS, SANS).

* Comparator(s)/control.
Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.
Controls are not relevant.

* Types of study to be included.
Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.
Included: Cross-sectional and longitudinal observational studies.
Excluded: treatment trials, conference abstracts, reviews, editorials, studies without original data.

Context.

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

* Main outcome(s).
Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

The effect size of 1) the relationships between negative symptoms and global functioning, 2) between negative symptoms and social functioning, 3) between negative symptoms and role functioning, 4) between individual negative symptom domains where data permits and a functioning measure (global, social, role).
Measures of effect
An estimated pooled effect size and 95% CIs for each study will be calculated and then presented by subgroup based on their respective association (i.e., Negative Symptom Total Scores and Global Functioning). The correlation coefficient (r) from each case will be normalized by converting the correlation coefficient to the Fisher's z scale and then all random effects meta-analyses will be performed using the transformed values. The results, will then be converted back to their respective effect size for results presentation. Most measures of effect will take place at baseline or at one time point within the study.

* Additional outcome(s).
List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

None.

Measures of effect None.

* Data extraction (selection and coding).
Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.
Data abstraction will be 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 ± SD), number of males/percent male, negative symptom scores (mean ± SD), negative symptom scale, and key findings associated with negative symptoms. For the meta-analysis, the following data will be 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-scores (t), p-values (p), (8) direction of effect, (9) negative symptom scale, (10) negative symptom variable (e.g., total score), (11) functioning scale

* Risk of bias (quality) assessment.

Describe the method of assessing risk of bias or quality assessment. State which characteristics of the studies will be assessed and any formal risk of bias tools that will be used.
Included studies will be independently evaluated for quality by two reviewers (A.B. and D.D.) and reconciliation of conflicts will be resolved by a third reviewer. Both cross-sectional and longitudinal studies will be assessed for quality using a modified Downs and Black instrument. The Downs and Black checklist utilizes 19-items to evaluate cross-sectional studies and 21-items for longitudinal studies, providing a total score out of 19 or 21 points for each study. Studies will not excluded from this systematic review and meta-analysis based on the quality assessments.

* Strategy for data synthesis.
Provide details of the planned synthesis including a rationale for the methods selected. This **must not be generic text** but should be **specific to your review** and describe how the proposed analysis will be applied to your data.
Due to heterogeneity between studies, DerSimonian and Laird random-effects meta-analyses will be performed on eligible studies to estimate pooled effect sizes and 95% CIs for each study and then will be presented by subgroup based on their respective association (i.e., Negative Symptom Total Scores and Global Functioning, Negative Total and Social Functioning, Negative Total and Role Functioning, Negative Domains and Functioning Measures). The correlation coefficient (r) from each case will be normalized by converting the correlation coefficient to the Fisher's z scale and then all random effects meta-analyses will
be performed using the transformed values. The results, will be converted back to their respective effect size for results presentation. Studies must have two or more independent samples with the same observations to be included in the aggregated meta-analysis. If applicable, scales will be inverted to match the direction of effect of the majority of scales. Statistical heterogeneity will be examined using the I^2 statistic, with I^2 > 50% deemed moderate, and I^2 >75% high heterogeneity. Stata version13 (StataCorp LP, College Station, Texas, United States) was used for all analyses with an $a<0.05$ for statistical significance.

* Analysis of subgroups or subsets.
State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.
None.
* Type and method of review.
Select the type of review and the review method from the lists below. Select the health area(s) of interest for your review.
Type of review Cost effectiveness No
Diagnostic No
Epidemiologic No
Individual patient data (IPD) meta-analysis No
Intervention No
Meta-analysis Yes
Methodology No
Narrative synthesis No
Network meta-analysis No

Pre-clinical No
Prevention No
Prognostic No
Prospective meta-analysis (PMA) No
Review of reviews No
Service delivery No
Synthesis of qualitative studies No
Systematic review Yes
Other No

Health area of the review Alcohol/substance misuse/abuse No
Blood and immune system No
Cancer No
Cardiovascular No
Care of the elderly No
Child health No
Complementary therapies No
Crime and justice No
Dental No
Digestive system No
Ear, nose and throat No
Education No
Endocrine and metabolic disorders No
Eye disorders No
General interest No
Genetics No
Health inequalities/health equity No
Infections and infestations No
International development No
Mental health and behavioural conditions Yes
Musculoskeletal No
Neurological No
Nursing No
Obstetrics and gynaecology No
Oral health No
Palliative care No
Perioperative care No
Physiotherapy No
Pregnancy and childbirth No
Public health (including social determinants of health) No
Rehabilitation No
Respiratory disorders No
Service delivery No
Skin disorders No
Social care No
Surgery No

Tropical Medicine No
Urological No
Wounds, injuries and accidents No
Violence and abuse No

Other registration details.
Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

Reference and/or URL for published protocol.
Give the citation and link for the published protocol, if there is one Give the link to the published protocol.
Alternatively, upload your published protocol to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.
No I do not make this file publicly available until the review is complete
Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

Dissemination plans.
Give brief details of plans for communicating essential messages from the review to the appropriate audiences.
Publication in Schizophrenia Bulletin or Schizophrenia Research and presentation at IEPA 2020 in Rio de Janeiro in Brazil.

Do you intend to publish the review on completion?
Yes

Keywords.
Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords will help users find the review in the Register (the words do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.
High Risk Psychosis; CHR; Negative Symptoms; Functioning

Details of any existing review of the same topic by the same authors.
Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.
None.

* Current review status.
Review status should be updated when the review is completed and when it is published. For newregistrations the review must be Ongoing.
Please provide anticipated publication date Review_Ongoing

Any additional information

Provide any other information the review team feel is relevant to the registration of the review.

Details of final report/publication(s).

This field should be left empty until details of the completed review are available. Give the link to the published review.