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THE COURSE OF AXIS I AND AXIS II DISORDERS IN CLINICAL HIGH RISK (CHR) ADOLESCENTS

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THE COURSE OF AXIS I AND AXIS II DISORDERS IN CLINICAL HIGH RISK (CHR) ADOLESENTS

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ABSTRACT

THE COURSE OF AXIS I AND AXIS II DISORDERS IN CLINICAL HIGH RISK (CHR) ADOLESENTS

Christy DaBreo-Otero

The detrimental impact of psychosis on individuals and society has sparked interest in early detection and intervention strategies to improve outcomes for those who are high-risk for developing psychosis. This study used data collected by the Recognition and Prevention (RAP) program to explore the progression of Axis I and Axis II disorders, clinical and functional characteristics, and predictors of conversion in a Clinical High Risk (CHR) sample. Using the RAP Program's classification system, participants were assigned to the following subgroups based on symptom presentation: Clinical High Risk Positive (CHR+) which is defined by the presence of attenuated positive symptoms and Clinical High Risk Negative (CHR-) which requires the presence of attenuated negative symptoms.

Participants consisted of 156 subjects (110 males and 46 females) who participated in the RAP Program during Phase I (2000-2006) and were separated into the high-risk groups: CHR+ and CHR-. These results indicated that Axis I disorders (mood, anxiety, substance use, and attention-deficit and disruptive behavior disorders) presented similarly at baseline in the CHR subgroups, however there were significant differences in the prevalence rates of paranoid personality disorder, borderline personality disorder, and schizoid personality disorder. In exploring the relationships between psychiatric

disorders, attenuated symptoms, and functioning, it was found that lower levels of role functioning were associated with mood disorders for CHR- participants. Additionally, social functioning and attenuated negative symptoms were found to have an impact on Cluster A personality presentation in both CHR subgroups. This study also explored the progression of psychiatric disorders, and results demonstrated that mood, anxiety, attention-deficit and disruptive behavior disorders, and personality disorders were persistent and recurrent from baseline to follow-up in both subgroups. Additionally, in examining predictors of conversion, positive symptoms were found to be the strongest predictor of conversion to psychosis and mood disorders were found to be a significant predictor of non-conversion.

The results from this study convey that CHR adolescents present with a constellation of diagnoses and symptoms. The findings suggest that it may be beneficial to continue to screen individuals diagnostically to develop specific intervention strategies based on how participants are assigned to high-risk groups.

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Chapter 1: Introduction

This dissertation contributes to an area of research that focuses on individuals who are clinical high risk (CHR) for developing psychosis. Specifically, this study will use data collected by the Recognition and Prevention (RAP) Program, a longstanding CHR Program in New York, to examine the baseline prevalence rates of co-occurring psychiatric disorders in a high-risk population and clinical and functional characteristics. Additionally, this study will explore which baseline characteristics predict conversion to psychosis and assess the long-term stability of psychiatric disorders in individuals who are at CHR in this cohort. The outcomes of these analyses may have important implications for prevention and/or treatment for high-risk populations.

Rationale and Significance

There has been emerging interest in the early detection and prevention of psychosis, in particular schizophrenia. There is considerable research demonstrating the debilitating effects of psychosis and the detrimental impact it has on an individual's quality of life. Individuals suffering from psychosis often experience cognitive difficulties, difficulties in maintaining interpersonal relationships, and role functioning problems such as academic and employment difficulties (Barch & Sheffield, 2014; de Waal, Dixon, & Humensky, 2018; Karambelas et al., 2018; McCann, Lubman, & Clark, 2011; Redmond, Larkin, & Harrop, 2010; Schaefer, Giangrande, Weinberger & Dickinson, 2013; Sheffield, Karcher, & Barch, 2018; Tolman & Kurtz, 2012). Unfortunately, this population is also susceptible to high mortality rates due to physical health problems and high rates of suicide (Castagnini & Bertelsen, 2011; Henderson,et al., 2015; Pompili et al., 2011; Suvisaari, et al., 2010). Due to these poor outcomes, over

the past twenty years there has been interest in prevention and developing criteria to identify individuals in this pre-psychotic phase of illness., as this may provide a window of opportunity for intervention. Terms such as “at risk”, “ high-risk”, “clinical high risk”, “ultra high risk”, and “prodromal” are used to categorize individuals in this phase in the ever growing literature on the subject.

Extensive research on the potential negative long-term outcomes of psychosis has propelled the prevention movement to gain momentum, calling for early intervention to begin as soon as possible, before psychosis becomes particularly disruptive to social, academic, and occupational functioning (McGorry, Killackey, & Yung, 2008). By targeting individuals who are at-risk for developing psychosis, we may be better able to identify factors that predict conversion to psychosis, which could in turn help to more readily inform early intervention strategies. Interest in early intervention research has led to the development of reliable and valid instruments which are used to identify individuals who are high-risk for developing psychosis. Many high-risk studies over the last several decades provided clues about predictors of conversion, and showed rates of conversion as high as 50%, with more recent rates between 17% and 35% (Fusar-Poli et al., 2012; Michel, et al., 2018; Miller et al., 2002; Yung et al., 2005). The decline in conversion rates may be attributed to false-positives, tailored intervention models, the promotion of early intervention programs, and the development of assessment measures (Yung and McGorry, 1996; Yung et al., 2007).

Many studies also suggest that there is a high co-occurrence of nonpsychotic disorders in individuals at-risk for psychosis. In fact, most help-seeking individuals cite nonpsychotic symptoms such as mood, anxiety, substance use, or behavioral problems as

their presenting concern which may overshadow high-risk symptoms (Falkenberg, et al., 2015; McAusland et al., 2017; Woods et al., 2009). Given the cooccurrence of other psychiatric disorders in this population and declining transition rates to psychotic disorders, it is important to investigate how co-occurring disorders impact the outcomes of those who do and do not develop psychosis.

Statement of Purpose

Using longitudinal data collected from the Recognition & Prevention (RAP) Program at Zucker Hillside Hospital, this study will assess the development of high-risk symptoms and potential associations with psychiatric disorders. Furthermore, to better understand the impact of psychiatric disorders on prodromal symptomatology and risk for conversion to psychosis, this study will assess how these disorders evolve in different stages of the prodrome.

Chapter 2: Literature Review

Rationale for Identifying Risk for Psychosis

Psychotic disorders are mental illnesses which are characterized by impairment in perception, emotional experiences, and behavior. Psychotic disorders affect about 3% of the population, with the onset typically occurring between the ages of 15 and 25. Psychotic disorders include schizophrenia (0.3-0.7%), schizophreniform disorder, schizoaffective disorder (0.3%), delusional disorder (0.2%), brief psychotic disorder, and other schizophrenia spectrum disorder. Individuals also can meet criteria for psychosis if diagnosed with a bipolar or depressive disorder with psychotic features or with a diagnosis of substance or medication induced psychosis (American Psychiatric Association, 2013).

Individuals who meet criteria for psychosis vary in their presentation due to their own unique combination of symptoms and experiences. Symptoms associated with schizophrenia are classified into two categories: positive symptoms and negative symptoms. Positive symptoms include hallucinations which are perception-like experiences that occur without an external stimulus and delusions which are fixed beliefs that are held despite evidence that suggests these beliefs may not be true. These symptoms are separate from negative symptoms, which include diminished emotional expression, avolition, and anhedonia which could lead to difficulties with attention, concentration, social and occupational functioning (American Psychiatric Association, 2000; Marder & Galderisi, 2017; Tsuang, Glatt, & Faraone, 2011).

It has been well documented that psychiatric comorbidities are common among people with schizophrenia. According to Buckley et al. (2009), anxiety symptoms are

common throughout the course of schizophrenia, with estimated prevalence rates of 15% for panic disorder, 29% for posttraumatic stress disorder, and 23% for obsessive compulsive disorder. It is also estimated that comorbid depression occurs in 50% of those affected by the illness. These nonpsychotic disorders accompanying schizophrenia make it challenging to form an accurate clinical picture of individuals who are affected. Moreover, it is unclear as to what extent these symptoms solely reflect psychological distress or are indeed unique features of a psychotic illness (Buckley et al., 2009).

There is substantial research to support that attention-deficit and disruptive behavior disorders and schizophrenia share similar symptomatology (Brodeur, Kiang, & Christensen, 2016; Donev et al., 2011; Niarchou et al., 2018; Oie & Rund, 1999; Salomon et al., 2011; Starc et al., 2017). The overlap in symptoms includes impulsivity, inattention, impairment in working memory, disorganized behavior, and emotion dysregulation, which can impact overall functioning and prognosis over time (Bae et al., 2010; Jobe & Harrow, 2010; Prouteau et al., 2015). Specifically, for ADHD, adolescents who carry this diagnosis are 4.3 times more likely to develop schizophrenia in the future in comparison to healthy controls (Dalsgaard et al., 2014). Additionally, externalizing behaviors such as conduct disorder are linked to the development of schizophrenia later in life (Rubino et al.,2009).

Individuals with schizophrenia often present with substance use and rates indicate that these individuals may engage in substance use at higher rates compared to the general population. Substances that are often reported are alcohol, nicotine, and cannabis, and opioids. (Khokhar et al., 2018; Winklbaur et al., 2006). As explained by Awad and Voruganti (2008), substance use is particularly dominant among individuals suffering

from schizophrenia, with approximately 50% meeting diagnostic criteria for a substance use disorder at some point in their lives. In addition, up to 25% of individuals with schizophrenia may be actively engaged in substance use at any given time during their illness (Awad, &Voruganti, 2012; Buckley & Meyer, 2009). For this population, increased substance use is associated with increased hospitalizations and low treatment compliance.

The symptoms and impairments associated with schizophrenia appear to be long-standing with periods of fluctuation in severity occurring over time (Hersen & Beidel, 2012). The course of schizophrenia is variable with symptoms wavering in severity and intensity (Jones, Hacker, Cormac, Meaden, & Irving, 2012; Perälä et al., 2007). As symptoms become more severe, it may be increasingly more difficult for people to stay in touch with reality, maintain relationships, and manage tasks required for daily living (Awad & Voruganti, 2012). According to Awad & Voruganti (2008) the early onset and chronic nature of schizophrenia often results in direct and indirect costs to the individuals affected and their family members and caregivers. Individuals affected are likely to encounter medical costs for hospital stays, out-patient care, rehabilitation, assisted living, and other health professional services. Other difficulties include loss of productivity, leading to unemployment. These indirect costs resulting from not being able to work can place a toll on these individuals, their families, and society. Caregivers report experiencing guilt, worry, shame, and feeling despair for themselves and their affected family member (Barker, Lavender, & Morant, 2001). Individuals with schizophrenia may also experience emotional suffering, social isolation, emotional distress, depression, and even premature death (Lindström, Eberhard, Neovius, & Levander, 2007). Because of

these substantial costs, there has been emerging interest in early detection and intervention strategies to alleviate, or if possible, prevent these outcomes.

Treatment options for schizophrenia include psychiatric medication and psychotherapy. Antipsychotic medications such as haloperidol, risperidone, and olanzapine have proven to be effective in combination with other therapeutic interventions such as such as CBT for psychosis (Dold et al., 2015; Lecomte 2015; Olivares, Pinal, & Cinos, 2011). Individual therapy, family therapy, and social skills training have also proven to be beneficial (Granholm, Holden, & McQuaid, 2014; Haddad, Brain & Scott, 2014). Although these forms of treatment continue to be helpful and beneficial for the positive symptoms of schizophrenia, oftentimes, patients are left with negative symptoms which account for severe difficulties in functioning and quality of life in addition to the costs of treatment such as hospitalization and medication (Patel, Cherian, Gohil, & Atkinson, 2014). Even with optimal treatment, persons with schizophrenia often continue to experience substantial impairment throughout much of their lives with many struggling with caring for themselves and others (Ofir et al., 2017).

In addition to the challenges listed above, individuals affected by psychosis are also highly stigmatized. The diagnostic label evokes perceptions that individuals with psychosis are dangerous, violent, and unpredictable (Corrigan & Kleinlein, 2005; Durand-Zaleski, Scott, Rouillon, & Leboyer, 2012). Furthermore, experiences of internalization of stigma may occur and can lead to emotional distress in the form of depression and anxiety which may have a detrimental impact on recovery, contribute to increased shame, and lower treatment adherence (Birchwood et al., 2007; Rusch et al., 2014). In conclusion, the debilitating effects of psychosis have ushered further

exploration of the period before the onset of full-blown psychosis to mitigate adverse long-term impact, improve symptoms, and boost functional outcomes.

The Psychosis Prodrome: A Historical Perspective

The onset of psychosis varies in length and can be characterized by nonspecific changes in thoughts, feelings, behaviors, and functioning. An individual who develops a psychotic disorder typically displays symptoms 1-2 years prior to the first psychotic break. The time period when symptoms preceding the onset of psychosis are developing is referred to as the prodromal period, and typically occurs during late adolescence or early adulthood (Häfner et al., 2003). As explained by Salokangas and McGlashan (2008) "the prodrome for psychosis is a retrospective concept referring mostly to the period from the first noticeable symptoms of unusual experiences to the first prominent psychotic symptoms" (p.95). The prodromal period can last several weeks, months or years while co-occurring with other disorders and leading to possible functional decline (Larson, Walker & Compton, 2010; Woods et al., 2010).

Presentation of symptoms include attenuated positive symptoms which are not severe enough to meet criteria for psychosis and precede full-blown psychosis. Prodromal symptoms are deviations in thinking patterns, behavior, and affect. Individuals in this phase may present with odd beliefs or unusual behaviors. They may have speech that appears vague, overly concrete, or disorganized. Others may note they have difficulty holding a conversation. Typically, attention problems, depression, anxiety, social difficulties, disorganization, and sleep disturbances emerge first, and then more specific attenuated psychotic experiences emerge later. Other common concerns include difficulties with memory and low motivation. Individuals may describe experiences

where they feel like their thoughts are disappearing, blocked, or coming very rapidly. There may be reports that others may know their thoughts possibly accompanied by increased suspiciousness. However, these thoughts are not at the intensity of paranoid delusions and the disorganized communication does not meet full criteria for a formal thought disorder (Goulding et al., 2013). Individuals may report experiences of others watching them, trying to harm them, or feeling fearful without any specific trigger. Individuals may also report losing interest in activities, becoming socially withdrawn, and displaying less affective expression. Although reports of perceptual experiences and ideations may arise, they do not meet the severity of delusions and hallucinations (Goulding et al., 2013). Family members, teachers, and others who interact more closely with the individual are likely to recognize changes in behavior. As these symptoms occur, individuals are likely to feel confused, frightened, and even doubt their experiences. These symptoms may present gradually over several months or years before a full onset of psychosis (Larson, Walker, Compton, 2010; Perkins, 2004). These changes may also impact a person's ability to remain focused in school, maintain stable employment and relationships, causing distress over time.

Individuals in the prodromal phase present with psychotic-like experiences which are different from full-blown psychosis in that the person questions or doubts their experiences. For example, a person may think that someone can read their mind and may be uncertain whether or not this experience is real or imaginary. As explained by Kline et al. (2012), the difference between psychotic and psychotic-like experiences lies in expression of doubt, conviction of reality of the experience. Generally, if these symptoms

persist, they may evolve into psychosis but not all psychotic-like experiences are predictive of full-blown psychosis.

To be in the prodromal phase implies that there will be a progression to psychosis. Much of the research on the prodrome has relied on retroactive studies, suggesting that conversion to psychosis is inevitable. However, there is ample research to suggest that the majority of help-seeking individuals do not go on to develop psychosis (Cannon et al., 2008; Cornblatt et al., 2003; Yung et al., 2004). Also, prodromal symptomatology is not just related to psychotic symptoms and can be non-specific, further highlighting that the presence of prodromal symptoms does not subsequently indicate conversion to psychosis. To reconcile this discrepancy, there has been a shift in the research field to replace the term prodrome with other terminology such as at-risk, high-risk, clinical high risk, and ultra high risk to accurately capture the vulnerability rather than imminency of psychosis (Fusar-Poli et al., 2013).

Conceptualizing the High-Risk Stage

In the last couple decades, there has been a considerable shift to understand the complexity and course of psychosis which has led to several advancements such as reliable and structured instruments to identify individuals at-risk, longitudinal studies to identify mechanisms and functional outcomes, and therapeutic and pharmacological interventions to delay or prevent onset of psychosis (Woodberry, Shapiro, Bryant, & Seidman, 2016). The diversity, complexity, and variedness of non-specific features of the prodrome coupled with the long-term impact of psychosis on cognitive, emotional, and social development have led to the development of several models to conceptualize the

high-risk state. These models provide criteria to assess symptoms to more accurately identify individuals at-risk and then to provide appropriate treatment.

Basic Symptoms. Early attempts to describe high risk symptoms were first made by Huber and Gross who identified basic symptoms as early manifestations of psychosis. These symptoms are essentially subtle subjective experiences of disturbance marked by changes in cognition, affect, and perception (Huber & Gross, 1989). This approach is based on retrospective studies on the prodrome and has gained widespread recognition in Germany and other parts of Europe as of the late 1990s. As explained by Larson, Walker, Compton (2010) basic symptoms are the first symptoms to develop and are "subjective experiences of thought, language perception, motor disturbances; impaired bodily sensations; impaired tolerance to stress; disorders of emotion, thought, energy, concentration and memory; and, disturbances in social functioning." (p. 4).

Basic symptoms manifest as subjective experiences and are rarely outwardly observed by others. This approach proposes that there are levels of progression of symptoms with subtle non-specific cognitive disturbances emerging first, then thought interference, speech difficulties, automatic skills deficits appearing later, and then lastly frank psychosis (Schultze-Lutter et al., 2010). These symptoms can be further assessed using the subscales: cognitive-perceptive basic symptoms (COPER) and cognitive disturbances scale (COGDIS). COPER requires the presence of at least one of ten basic symptoms within the last three months and COGDIS requires the presence of at least two of nine basic symptoms within the last three months (Schultze-Lutter & Theodoridou, 2017).While this approach is not widely recognized in the United States, it has

influenced the development of other high-risk models which will be further expanded on below.

Ultra High Risk. The basic symptom approach helped to lay the groundwork for high-risk research and also revealed some shortcomings in the current methodological approaches at the time. For instance, many subjects in research studies were incorrectly labeled as at risk for psychosis but did not actually develop psychosis (Falloon, 1992; Yung & Nelson, 2013). Previous studies also further highlighted the challenges of prospectively identifying individuals in the prodromal state due to nonspecific nature of prodromal symptoms. The ultra high risk (UHR) approach arose out of the need to minimize the concerns surrounding the false-positives and to widen the risk criteria to identify high-risk groups.

The UHR approach considers the age of the individual acknowledging that psychotic symptoms tend to appear in adolescence or early adulthood, specificity of symptoms, and genetic and clinical risk factors in identifying those at risk. Additionally, the name ultra high risk, also distinguishes help-seeking individuals from other high-risk groups such as those who may have a genetic risk. As explained by Yung & Nelson (2013), to meet UHR criteria, the individual must be between the ages of 15 and 25 years old, experience a decrease in functioning for at least one month or sustained low functioning during the past year, and meet criteria for one of the following groups: attenuated positive symptom syndrome (APS), brief limited intermittent psychotic syndrome (BLIPS), and trait vulnerability group. To meet criteria for APS, there must be the presence of attenuated psychotic symptoms within the past year. Individuals must endorse at least one of the following symptoms such as odd beliefs or magical thinking,

ideas of reference, perceptual disturbance, paranoid ideation, odd behavior or appearance, odd thinking and speech at the high-risk level. To meet criteria for BLIPS, individuals must endorse the same symptoms, but at a psychotic level of severity for a brief duration. These transient symptoms should last for less than one week and resolve spontaneously within a year. To meet criteria for trait vulnerability, an individual must present with a genetic vulnerability to a psychotic disorder such as having a family history of a psychotic disorder in a first-degree relative or the individual meeting diagnosis for schizotypal personality disorder.

These ultra high risk categories were used to create the Structured Interview for Prodromal Syndromes (SIPS) along with its companion Scale of Prodromal Symptoms (SOPS) which were developed by McGlashan and colleagues at Yale University and are widely used in the United States. According to McGlashan, Walsh and Woods (2010), the SIPS and SOPS were developed to identify the presence/absence of one or more of the psychosis risk-states; to measure the severity of risk symptoms cross-sectionally and longitudinally; and to define the presence/absence of psychosis. The SIPS also consists of the Criteria of Prodromal Syndromes (COPS) which provides operationalized definitions of the clinical high risk (CHR) syndromes: attenuated positive symptom syndrome (APS), brief intermittent psychotic syndrome (BIPS), and genetic risk and deterioration syndrome (GRD).

Clinical High Risk. The Clinical High Risk (CHR) approach has incorporated ultra high risk criteria since its inception and also provides the basis for this current study. The Clinical High Risk approach developed by Cornblatt and colleagues at the Recognition and Prevention (RAP) Program proposes that high-risk symptoms progress

along a continuum and uses the SIPS and SOPS as the basis for this classification (Cornblatt et al., 2003).

Compared to previous pioneers such as McGorry, Yung and colleagues, the RAP Program is unique as it incorporates a neurodevelopmental perspective to track the longitudinal progression of high-risk symptoms over time. As explained by Cornblatt (2002), the neurodevelopmental model of schizophrenia proposes that psychosis is the result of structural, functional, and biochemical abnormalities occurring during prenatal development. These abnormalities lead to a biological vulnerability which presents as cognitive deficits, affective symptoms, social isolation, and school failure. Subsequently, genetic, biological, or environmental triggers may then cause positive symptoms to develop which may lead to full-blown psychosis. Cornblatt et al (2015) explains that there are three stages: The first stage or pre-illness phase is marked by neurocognitive deficits, followed by the prodromal phase where behavioral changes are observed, and then the final stage of full-blown psychosis (See Figure 1).

Early studies focused on the prodrome as a single entity, leaving very little room for the possibility of multiple pre-psychotic phases. The RAP program's classification system shifted the way the prodromal phase is viewed by focusing on developmental stages. The RAP program's classification system is grounded in the staging theoretical framework which has been widely used in medicine but only recently applied to studying the psychosis risk syndrome (McGorry et al., 2007). Using the SIPS, the RAP Program developed criteria to classify individuals at high-risk based on the presence of positive and negative symptoms (Cornblatt et al., 2003). According to Cornblatt and colleagues, there is an early period and late period in the prodromal phase of illness. In the early

prodromal phase, attenuated negative symptoms and affective symptoms begin to emerge, affecting an individual's functioning. The late prodromal phase is defined by the development of attenuated positive symptoms. For some individuals, the symptoms then progress to psychosis.

This developmental model proposed by Cornblatt and colleagues provides a number of different entry points into the prodrome and is categorized by stages. During the first stage referred to as Clinical High Risk Negative (CHR-), individuals may present with nonspecific, attenuated negative symptoms such as increased social isolation, school failure, decreased expression of emotions, and rigid thinking. For this stage, individuals must score at least a 3 on the SOPS on the negative symptom scale, signifying moderate to severe intensity. This stage is then followed by the Clinical High Risk Positive (CHR +) stage where individuals present with attenuated positive symptoms with a SOPS score between 3 and 5. Symptoms reported may include disorganized speech, unusual thought content, cognitive changes, and perceptual abnormalities. The final category which is schizophrenia like psychosis (SLP), requires that an individual present with at least one psychotic level symptom (6 on the SOPS) but they do not meet full criteria for schizophrenia (Lencz, et al., 2004). For the purposes of this study, we will be focusing only on the CHR+ and the CHR- subgroups (See Figure 2).

This model allows one to track the progression of the illness over time, which also helps to inform stage-specific interventions. This also leaves space to further develop criteria to identify early risk factors for high-risk individuals. Research regarding appropriate interventions for high-risk individuals is crucial given the indeterminate nature of the high-risk state, the fact that the majority of high-risk individuals will never

develop psychosis, and the issue that many medications, namely antipsychotic medications, carry serious side effect risks (Corcoran, Malaspina, & Hercher, 2005). The choice of intervention in the prodrome is further complicated by the presence of frequent psychiatric comorbidities in high-risk individuals.

Validity of High-Risk Syndromes

In studies detecting psychosis risk, high risk groups that are often referenced are ultra high risk (UHR) and clinical high risk (CHR). UHR is mostly used in Europe and Australia and is assessed by using the CAARMS, whereas, CHR is frequently used in North America and is assessed by the SIPS. Despite, some differences in the types of instruments used to assess risk, CHR and UHR are fairly similar in their categorization of high-risk individuals (Correll, Hauser, Auther, & Cornblatt, 2010; Miller et al., 2003). Both the SIPS/SOPS and CAARMS assess positive symptoms, negative symptoms, disorganization symptoms, and general symptoms (Correll, Hauser, Auther, & Cornblatt, 2010).

Several studies have been conducted to evaluate the diagnostic validity of the prodromal risk syndromes described above. The SIPS was first tested for validity in 2000, with the results showing that 46% of the participants who met at-risk criteria developed schizophrenic psychosis after 6 months, and 54% at 12 months (Miller et al., 2003). In a more recent study, the validity of the SIPS was assessed using a pooled sample from 8 academic research centers in North America: Emory University, Harvard University, University of California Los Angeles, University of North Carolina, University of California San Diego, University of Toronto, Yale University, and Zucker Hillside Hospital who are part of the North American Prodrome Longitudinal Study

(NAPLS) consortium. Results demonstrated that, of the 291 participants who completed follow-up, 82 converted to psychosis over 30 months. The cumulative prevalence rate of conversion to psychosis was 35.3% over this time period (Cannon et al., 2008). In another NAPLS study evaluating predictive validity, prodromal risk participants were compared to several groups (e.g. normal controls, help-seeking controls, familial risk subjects, and subjects with schizotypal personality disorder) on different domains such as functioning, follow-up outcome, and symptom profile (Woods et al., 2009). Overall, the results showed that the prodromal risk participants were more symptomatic compared to the other groups and were more likely to convert to psychosis over a 2-year period. These findings support the diagnostic validity of this risk syndrome for psychosis (Woods et al., 2009).

The use of valid and reliable assessment tools has been a critical step towards early identification and intervention strategies for high-risk individuals. The advancement in assessment tools have led the way to improving recruitment strategies, identifying symptoms, and increasing our understanding of the high-risk clinical presentation.

Early Intervention Programs

Early intervention research for psychotic disorders is viewed as having the potential to produce better outcomes in individuals vulnerable to developing psychosis and to reduce some of the clinical and economic burdens associated with the illness (Fusar-Poli et al., 2013; Stafford, Jackson, Mayo-Wilson, Morrison & Kendall, 2013). This line of logic is deeply rooted in preventative medicine research.

Mrazek and Haggerty (1994) described some of the challenges in the classification system used to categorize prevention for physical illnesses. They pointed

out that the previous categorization primary, secondary, and tertiary prevention is ambiguous when applied to the prevention of progression of mental illness as it is unclear how prevention measures are implemented when there is no clinically diagnosable disorder. These researchers reorganized the classification system into universal prevention, selective prevention, and indicated prevention. Indicated prevention, which targets high risk individuals who present with minimal but detectable symptoms is of particular importance in early intervention research as it targets individuals who are of especially high risk of developing serious mental disorders such as psychosis (Mrazek & Haggerty, 1994, p.22-24).

Within the last 30 years there has been emerging interest in indicated prevention which has paved the way for high-risk research and treatment by helping researchers and clinicians explore methods to prevent or postpone the onset of psychosis and develop treatment options to address presenting symptoms. Ideally, indicated prevention may provide potential benefits where help-seeking individuals either return to their previous level of functioning or maintain their current level of functioning (Correll, Hauser, Auther, & Cornblatt, 2010; Fusar-Poli et al., 2016). The field of prevention research is exciting as it sheds light on the development and course of psychotic illness. It also involves identifying individuals who are in the pre-psychotic phase of illness, meaning that they are presenting with prodromal or high-risk symptoms.

Early intervention programs consist of a multidisciplinary team of mental health professionals who provide therapeutic and psychopharmacological interventions that are tailored to the needs of help-seeking individuals (McGorry, Killackey, & Yung, 2007). High-risk research and treatment programs have proliferated around the world and been

largely successful and informative in increasing our understanding of high-risk states. Australia and some parts of Germany were the front runners for early intervention programs, but now there are many programs that can be found in the United States, Canada, and Asia. These programs vary in their methodological approaches, assessments, and duration while offering support to help-seeking individuals and their families/caregivers (McGorry, Killackey, & Yung, 2008).

Effective treatments have been identified through these early intervention treatment programs. For instance, cognitive therapy, which has been shown to be effective in mitigating effects of psychosis may also reduce the severity of psychotic symptoms in young individuals when utilized as a preventative intervention (Morrison et al., 2012). Comparatively, in another study conducted by McFarlane et al (2015), a therapeutic intervention called Family-aided Assertive Community Treatment (FACT) was proven to be effective in improving negative, disorganized, and general symptoms. Other studies have investigated potential beneficial effects of omega-3 fatty acids on preventing onset of psychosis (Amminger, et al., 2015; Mosshaeb, 2012). Additionally, a meta-analysis assessing the efficacy of early intervention treatment options revealed that omega-3 and CBT demonstrated good effect in reducing transition rates in high- risk participants. Antipsychotic medications were mostly found to be somewhat effective in delaying conversion to psychosis, but are associated with side effects and high attrition rates. (van der Gaag et al., 2013).

It is also noteworthy that in North America, many sites have collaborated to form the aforementioned NAPLS which is a consortium of eight early intervention programs in North America. Sites participating in the NAPLS consortium contributed their

preexisting data sets to form a larger sample of CHR individuals with more power to further assess outcomes. These early intervention programs have largely contributed to high-risk research by exploring treatment options, neuropsychological profiles, and risk algorithms for CHR individuals. Treatment outcomes from recent NAPLS studies have revealed that CHR participants are more likely to report experiencing stressful life events and to experience daily hassles (Trotman et al., 2014) and also report higher baseline cortisol levels compared to healthy controls (Walker et al., 2013). Based on several NAPLS studies, there are observed impairments in functioning for CHR individuals (Fusar-Poli et al., 2013; Piskulic et al., 2016; Seidman et al., 2010; Seidman et al., 2016; Velthorst, 2019). Cornblatt et al. (2012) found that social and role functioning remained relatively stable in CHR subjects who converted to psychosis. In contrast, role functioning improved over time in nonconverters. Additionally, using multivariate models, NAPLS studies have identified biomarkers (e.g., neuroimaging and electrophysiology) and predictive algorithms to more accurately identify predictors for conversion (Cannon et al., 2016). This consortium went on to collect prospective genetic samples and conducted further research on the biological underpinnings of psychosis.

The Recognition and Prevention (RAP) Program. A program founded by Barbara Cornblatt in 1998 and is one of the first early intervention programs in North America to investigate and treat individuals who are high risk for psychosis. Since its inception, the program has contributed to research on the progression of symptoms in CHR individuals while offering educational resources and treatment options for young adults and their families.

Research studies of the RAP Program have focused on identifying vulnerability markers that may be unique to CHR individuals. Studies from the RAP Program have specifically concentrated on social functioning, role functioning, and overall neurocognitive functioning using a variety of testing batteries and assessments. RAP studies consistently demonstrate that CHR individuals report significant impairments in social and role functioning suggesting that these impairments may serve as potential risk factors (Carrión et al., 2011, 2013; Cornblatt et al., 2012; Olvet, Carrión, Auther, & Cornblatt, 2015). In a study conducted by Carrión et al. (2018) comparing baseline neurocognitive performance across different groups (healthy controls, CHR individuals, and individuals in the early first- episode phase of psychosis), it was found that verbal learning impairment was most predictive of conversion to psychosis. This finding is noteworthy, implying that verbal learning may be a vulnerability marker and could inform specific interventions for high-risk individuals. Additionally, CHR individuals who did convert to psychosis presented with similar functioning compared to those subjects in the early first-episode phase of psychosis, supporting the likelihood of functioning declining during the progression of psychosis (rather than as a result of psychosis). In another study comparing CHR subjects to healthy controls, CHR subjects highlighted that auditory mismatch negativity (MMN) may impact baseline functioning and is negatively correlated with reading ability, social and role functioning (Carrión et al., 2015). Other studies have found that longer duration of negative symptoms to be associated with poorer social functioning, severity of attenuated positive symptoms to be a predictor of conversion to psychosis, and disorganized symptoms, impaired social

functioning, and low processing speeds to predict poor social functioning (Carrión et al., 2016; Carrión et al.,2013).

Using the framework of the RAP model, this study aims to further explore the progression of symptoms in CHR subjects and how clinical profiles may evolve during different stages of the model.

Psychiatric Comorbidities in High-Risk Populations

As mentioned previously, the psychiatric comorbidities with schizophrenia have been well-documented. Given the cooccurrence of nonpsychotic disorders with high- risk symptoms, it is important to examine the prevalence rates, progression of these disorders, and functional outcomes in high-risk youth. It is essential to accurately identify comorbid disorders as this has implications for early intervention and treatment options. This study will assess the course of Axis I and Axis II disorders using DSM-IV criteria, which was in use at the time of data collection.

Prevalence of Axis I Disorders

Mood and Anxiety Disorders. Similar to findings in schizophrenia research, affective and anxiety disorders are frequently observed in the high-risk population and may prompt help-seeking individuals to seek treatment.

An earlier retrospective study of the schizophrenia prodrome conducted by Hafner and colleagues (1998), identified depression as the most frequently endorsed symptom preceding the onset of psychosis. Hafner and colleagues suggested that depression might actually be an expression of the development of psychotic illness process. Later studies assessing the progression of depressive symptoms confirmed that depression may impact psychosis onset (Yung et al., 2007).

A recent meta-analysis of prospective high-risk studies found that about 73% of at-risk participants had at least one comorbid Axis I diagnosis, with the most common being depressive and anxiety disorders (Fusar-Poli et al., 2014). Research findings show that non-bipolar mood disorders appear to be prevalent in the high-risk population. Fusar-Poli et al. (2014) found that 41% of high-risk subjects met criteria for a depressive disorder. In a NAPLS study consisting of 377 participants, 55% met criteria for a depressive disorder (Woods et al., 2009). In another study assessing transition to psychosis in a CHR sample, it was observed that 34% of participants met criteria for a depressive disorder (Salokangas, et al., 2012). Among several high-risk studies, major depressive disorder appears to be the predominant mood diagnosis in this population (Kline et al., 2018; Lin et al., 2015; Meyer et al., 2005; Rosen et al., 2005; Salokangas, et al., 2012). Depressed mood appears to be associated with poor role and social functioning (Fulford et al., 2013). In another study assessing the prevalence of depressive disorders, CHR participants with current or past depression also demonstrated more impairments in functioning and more severe negative symptoms (Kline et al., 2018).

Anxiety is also commonly observed in the CHR population (Addington et al., 2011; Fusar-Poli et al., 2014; Woods et al., 2009). In one study consisting of a CHR sample of 765 subjects, 51% met criteria for an anxiety disorder with social phobia being the most common. (McAusland et al., 2017). Other studies have replicated similar findings of social phobia being the most prevalent of all anxiety disorders among high-risk individuals (Hui et al., 2013; Meyer et al., 2005; Svirskis et al., 2005).

Several longitudinal studies have been conducted to assess obsessive compulsive disorder (OCD) in high-risk individuals. One study revealed sizable prevalence rates of

20% in high-risk youth, but after 12 months none of the individuals diagnosed with OCD converted to psychosis (Niendam et al., 2009). In contrast, in another study with a 12-month follow-up, OCD symptoms at baseline predicted incident diagnosis of a psychotic disorder at 12-month follow-up, showing that when attenuated psychotic symptoms are accompanied by OCD symptoms, the risk for transition to psychosis increases (Van Dael et al., 2011). Another study found that a diagnosis of incident OCD was associated with higher rates of psychotic disorders at 7-year follow-up (Fontenelle, 2011). Fontenelle and colleagues (2012) completed another study a year later where they assessed markers for vulnerability to OCD with results demonstrating that participants who presented with OCD and psychosis after the 7-year follow-up period displayed more severe levels of depression and anxiety after conversion to psychosis.

Studies exploring the occurrence of comorbid Axis I disorders at baseline in at risk participants found that common baseline diagnoses are major depressive disorder (50%), anxiety disorders such as anxiety disorder not otherwise specified (NOS; 17%), obsessive compulsive disorder (6.4%), and social phobia (17%; Fontenelle et al., 2011; Meyer et al., 2005). In another study assessing the prevalence of depressive and anxiety disorders in at-risk mental state (ARMS) participants, 40% of participants had a comorbid depressive disorder, 8% had an anxiety disorder and 14% of participants had both a depressive disorder and anxiety disorder (Fusar-Poli et al., 2014). These studies confirm the common occurrence of anxiety and depressive disorders in high-risk populations.

Attention Deficit and Disruptive Behavior Disorders. The well-documented research on the overlap of symptoms associated with ADHD, disruptive behavioral

disorders, and psychosis has also led to further research on how these symptoms manifest before the onset of full-blown psychosis. Many individuals who are high-risk for developing psychosis also present with ADHD diagnoses, externalizing behaviors, and academic concerns (Karatekin, White, & Bingham, 2010). As explained by Simeonova, Nguyen, and Walker (2014) "The general pattern of findings suggest that pre-psychotic youth are more socially isolated, withdrawn, emotionally labile, anxious, and aggressive than their healthy siblings and/or age-matched comparison subjects. They also have higher levels of impaired attention, which remain stable and elevated from childhood to adolescence, and are assumed to negatively affect social interactions leading to increased stress related to social situations" (p.2). Some studies even suggest that ADHD may be a vulnerability marker for psychosis but findings are inconsistent (Diwadkar, et al., 2011; Keshavan et al., 2003).

There is evidence that inattention difficulties manifest for help-seeking individuals who are high-risk (Francey et al., 2005; Pukrop et al., 2007; Simon et al., 2007). Hurtig et al (2011) linked psychotic-like experiences to inattentive symptoms (Hurtig et al., 2011). An earlier study conducted by Mazzoni et al (2009) demonstrated that childhood-onset disorders were prevalent in young adults who met criteria for being in the pre-psychotic phase. In this relatively small sample of 9 participants, diagnoses that were endorsed included ADHD, elimination disorders, oppositional defiant disorder, enuresis or encopresis, conduct disorder, separation anxiety, and transient tic disorder. These findings support the viewpoint of a developmental perspective when exploring the progression of symptoms in the high-risk state.

Recent studies have further explored the connection between disruptive behavioral disorders and identifying at risk youth. A more recent study conducted by Simeonova et al.(2014), investigated whether or not parents' report of social and behavioral problems on the CBCL (Child Behavior Checklist) can be used to identify at risk youth. Results indicated that the CBCL scales: Withdrawn/Depressed and Thought Problems were the most useful in identifying at-risk youth which has implication for developing future screening measures.

Substance Use. Research on the patterns and rates of substance usage in high-risk individuals varies which has led to interest in clarifying the relationship between substance use and transition to psychosis. There are also differences in reports of rates of substance abuse and dependence cooccurring within the pre-psychotic phase but the consensus appears to be that cannabis, nicotine, and alcohol are the most commonly reported used substances in CHR populations (Addington et al., 2014).

Varying rates of cannabis use and cannabis use disorders has been observed in high-risk samples. Phillips et al., (2002) found that 37% of subjects reported using cannabis at least once and 18% of subjects met criteria for cannabis dependence. Corocan et al. (2008) observed that 41% of high-risk individuals endorsed cannabis use. Several studies also compare cannabis use to use of other substances, citing varying rates among high-risk participants. In a study conducted by Auther et al. (2015) baseline comparisons revealed that alcohol use was reported in 45.3% of CHR youth and cannabis use rates were 38.1%. Additionally, 85% of participants who reported cannabis use also reported alcohol use, implying that individuals in this population are likely to use multiple substances. In another study, at-risk participants reported increased tobacco, alcohol

and cannabis use compared to controls and a noteworthy finding was that at-risk status was significantly associated with higher alcohol use (Carney et al., 2017). Findings from Buchy et al. (2014) cited that CHR participants endorsed more significant cannabis and tobacco use and lower alcohol use over a one-year period. Also, in comparison to healthy controls, CHR youth were more likely to report higher prevalence rates and frequencies of cannabis use, the age of onset of use was younger, and they were more likely to use cannabis alone. However, Russo et al. (2014) observed that healthy controls reported higher cannabis use but lower alcohol use compared to high-risk individuals. It also appears that use of more elicit substances is uncommon among CHR youth (Addington et al., 2014; Buchy et al, 2015).

Prevalence of Axis II disorders

Research concerning personality pathology in at-risk participants is scarce but there is evidence suggesting that schizotypal personality disorder (SPD) traits are similar to the characteristic symptoms of schizophrenia, but are less severe (Ericson, Tuvblad, Raine, Young-Wolff & Baker, 2011). The criteria for SPD can be separated into three symptom dimensions (positive, negative, and disorganized) which are also consistent with the diagnostic criteria for schizophrenia. Since, the criteria for SPD may be attributed to a genetic loading or vulnerability to developing schizophrenia, it is actually ideal for use in identifying individuals at-risk for psychosis. In fact, several strategies have been used based on these criteria. Individuals are considered to meet at-risk syndromes if they experience a recent onset of attenuated psychotic symptoms including at least one of the following SPD symptoms: ideas of reference, odd beliefs, magical

thinking, perceptual disturbance, odd thinking and speech, paranoid ideation, and odd behavior or appearance.

High-risk symptoms and SPD shares some similar features but SPD is an independent syndrome. The major distinguishing feature is that SPD is thought to be longstanding and stable while high risk symptoms are thought to be progressing. However, there are major gaps in the literature regarding the stability of this disorder. There is a study conducted by Ericson and colleagues in 2011 which investigated the genetic and environmental etiology of SPD traits in adolescent twins. These individuals were identified as presenting with SPD traits and were assessed on two occasions between the ages of 11 and 16 years old. They found genetic variance in the SPD traits with moderate stability in SPD traits between early to middle adolescence. The researchers suggested that future studies of schizotypal traits in individuals with prodromal symptoms need to further explore other factors that may be operating (Ericson et al., 2011)

While the research does suggest that the most common Axis II diagnosis is schizotypal disorder for high-risk individuals with a prevalence rate of 21%, there is some evidence that other personality disorders are present for this group as well. In a study reporting on high-risk participants who did not convert to psychosis, Addington et al. (2011) looked at Axis I and Axis II diagnoses and found that 29% of the sample had consistent diagnoses at baseline and follow-up of avoidant, borderline, schizotypal, and paranoid personality disorders and 14% had emerging diagnoses of avoidant, borderline, and obsessive compulsive personality disorders at follow-up. These findings also encourage further exploration of personality disorder development over time.

Borderline personality disorder (BPD) has also observed in high-risk individuals. Some of the symptoms associated with BPD are similar to attenuated positive symptoms which are essential in establishing high-risk criteria. There is evidence to suggest that individuals with BPD are likely to experience hallucinations, body image distortions, and ideas of reference, especially during stressful periods (Thompson et al., 2012). The prevalence rates for BPD in high-risk individuals are inconsistent with reports as low as 5% or as high as 17% (Lencz et al., 2004; Rosen et al., 2006). More recently Ryan et al. (2017) reported prevalence rates of 25%. Although Rosen and colleagues found prevalence rates of 17% for BPD, there was no difference in prevalence rates of their high-risk sample compared to their control sample. Based on these findings, it remains unclear if there is a true difference in presentation of this disorder and how it contributes to our understanding of personality disorder pathways that may be linked to the development of psychosis.

Thompson and colleagues attempted to further explore these issues, finding that there was no difference in the rates of transition to psychosis in individuals with baseline BPD compared to those without the diagnoses. In addition, reports of BPD symptoms at baseline were not related to the onset of a particular psychotic disorder.

With limited research, it still remains unclear as to whether or not there is a distinction between individuals whose high-risk symptoms are manifested in their personality framework and individuals who are truly at risk for psychotic disorders. This study hopes to clarify how personality disorders present in different high-risk stages.

Attenuated Positive and Negative Symptoms

Individuals who are high-risk for psychosis may experience attenuated positive and negative symptoms in addition to psychological difficulties which may induce further distress. While there is considerable research on how positive and negative symptoms present and develop in this population, less is known about the relationship between attenuated symptoms and co-occurring psychiatric disorders (Carrion et al., 2016; Davies et al., 2018, Lencz et al., 2004).

Anxiety and mood disorders have been found to be strongly associated with attenuated positive symptoms and negative symptoms (Addington et al., 2011). Some studies suggest that high-risk individuals who meet criteria for anxiety disorder or depression are more likely to endorse worsening negative symptoms (Falkenber et al., 2015; McAusland et al., 2015). Individuals who meet criteria for anxiety disorders, depressive disorders, or both are more likely to endorse attenuated positive symptoms such as suspiciousness (McAusland et al., 2017). There is also evidence to support that anxiety disorders are related to certain attenuated positive and negative symptoms such as hallucinations and withdrawal, and blunted affect (Lysaker & Salyers, 2007).

Few studies have explored the relationship between substance use and attenuated symptoms. One longitudinal study examining the relationship between substance use and clinical measures found a link between cannabis use and hallucinations/perceptual disturbances which are positive symptoms. In this study it was also observed that positive symptoms worsened with increase in cannabis use and improved or remitted when high-risk individuals stopped cannabis use altogether (Corcoran et al., 2008). Similarly,

findings from Wade et al (2007) determined that heavy substance use was associated with attenuated positive symptoms.

Cluster A personality disorders (schizoid, schizotypal, paranoid personality disorders) share symptoms that may overlap with attenuated positive and negative symptoms. In particular, schizotypal personality disorder is used as a marker to identify individuals who are high-risk for psychosis and is characterized by positive symptoms such as suspiciousness, odd thinking, perceptual disturbances and negative symptoms such as inappropriate affect, diminished emotional expression, social anhedonia, and avolition (Esterberg et al., 2010). Zoghbi and colleagues confirmed this in a study consisting of a sample where SPD was highly prevalent and found to be associated with attenuated positive and negative symptoms (Zoghbi et al, 2019). A defining feature of paranoid personality disorder is suspiciousness, which is a positive symptom and schizoid personality disorder consists of negative symptoms such as avolition, flat affect, and social anhedonia (American Psychiatric Association, 2000). As these personality disorder traits present with similar features of positive and negative symptoms, it is expected that Cluster A personality disorders will be associated with attenuated positive and negative symptoms.

Studies exploring the relationship between attention-deficit and disruptive behavior disorders and attenuated symptoms in high-risk populations are scarce. There is evidence to suggest that high-risk individuals with these disorders are emotionally labile, present with disorganized communication, and are inattentive which are similar features of positive and negative symptoms (Miller et al., 2002). One study investigating social and behavioral problems on the CBCL found that the Withdrawn/Depressed scale closely

resembled negative symptoms and the Thought Problems scale resembled positive symptoms and are useful instruments for identifying at-risk youth (Simeonova et al., 2014).

In this study we hope to further explore the relationships between psychiatric disorders and attenuated positive and negative symptoms. We expect that psychiatric disorders will be associated with higher levels of attenuated positive and negative symptoms. We also hope our findings will help to further clarify these relationships.

Social and Role Functioning

For many high-risk individuals, social and role functioning difficulties manifest before first-episode psychosis and the impact may be more noticeable than the actual attenuated positive and negative symptoms (Addington & Addington, 2005). The development of high-risk symptoms may cause individuals to isolate themselves from peers, feel "othered", and disconnected from themselves. These symptoms may also impact academic achievement, success, and completing tasks for work and school. Although social and role functioning is widely studied in high-risk individuals, less is known about the relationship between functioning and psychiatric disorders in this population. Based on the pre-existing literature, we do expect there to be lower levels of social and role functioning associated with mood disorders, anxiety disorders, attention-deficit and disruptive behavior disorders, and personality disorders.

Earlier studies on the prodrome have cited impairments in social and role functioning in conjunction with mood and anxiety disorders to be defining characteristics of the prodrome (Yung and McGorry, 1996). Comorbid anxiety and depressive disorders coupled with the at- risk symptoms have an adverse impact on baseline functioning levels

in the participants. For anxiety disorders, social anxiety in particular is associated with lower levels of social functioning. (Chudleigh et al. 2011). One study clarifying this relationship suggests that dysphoric mood is associated with lower levels of role and social functioning (Fulford et al, 2013). It has also been found among CHR participants that participants with current and past depressive histories present with more significant impairments in social functioning compared to those participants who did not have a history of depression (Kline et al., 2018). The experience of anxiety and mood disorders could further exacerbate social functioning deficits, leaving individuals feeling dissatisfied with their social connections. Additionally, less severe mood and anxiety disorders are associated with improvement in both social and role functioning, suggesting that anxiety and mood disorders may indeed be contributors to social and role function deficits in high-risk groups (Schlosser et al., 2012).

Attention-deficit and disruptive behavior disorders are also associated with lower levels of social and role functioning in adolescents, evidenced by deficits in executive functioning and emotional processing. Individuals in the prepsychotic phase may display low frustration tolerance, impulsive behavior, have difficulties with focus and attention making it difficult to perform well in school and maintain close connections with peers (Cadesky, Mota, & Schachar, 2000; Marsh & Williams, 2006).

In examining the relationship between substance use and functioning, Auther and colleagues compared substance use in CHR participants to healthy controls. Lifetime CHR cannabis users reported higher social functioning, CHR cannabis users had higher social functioning compared to nonusers at follow-up and reported no significant differences in role functioning (Auther et al., 2012). In another study, adolescents who

had an earlier onset of cannabis use disorder (before age 15) demonstrated better social functioning and were more likely to perform poorly academically (Compton et al., 2011). Similarly, in another study, early onset of cannabis use was associated with higher levels of social functioning compared to nonusers (Bagot, Milin, & Kaminer, 2015). Based on these findings, it appears that cannabis use is related to better social functioning.

Personality disorders impact the ability to get along with others and perform well academically and in work environments. The role of social and role functioning is included under the general diagnostic criteria in the DSM-IV-TR (American Psychiatric Association, 2000) specifying that this "enduring pattern leads to clinically significant distress or impairment in social, occupational, or other important areas of functioning " (p.689). However, this is not specifically included as diagnostic criterion for each of the personality disorders. Oltmanns and colleagues explored the relationship between social functioning and personality disorders. In a sample of 577 participants, 33% met criteria for a personality disorder. Results indicated that impairment in social functioning is associated with personality pathology. More specifically, participants who endorsed a Cluster A personality disorder (paranoid, schizoid, and schizotypal) also reported lower social functioning (Oltmanns et al., 2002).

Predictors of Conversion

Although the majority of individuals in a high-risk sample do not transition to psychosis it is still imperative to identify these predictors to inform early intervention treatment and also provide important information about converters and non-converters.

Several studies highlight that positive symptoms are the most robust and reliable predictors of conversion (Cannon et al., 2008; Gee & Cannon, 2011; Ruhrmann et al.,

2008; Yung et al., 2003). A study analyzing baseline demographics and clinical predictors of psychosis in a CHR sample, reported that higher SIPS scores on positive symptoms were predictive of conversion, suggesting that the severity of positive symptoms may be associated with more severe psychosis. (Zhang et al., 2017).

There is evidence to support that anxiety disorders are not predictors of conversion. In a large-scale study of 509 at-risk subjects, exploring comorbid diagnoses and their impact on transition outcomes, it was found that anxiety disorders did not have an impact on transition to psychosis (Fusar-Poli et al., 2014). In another study conducted by McAusland et al (2014), 51% of CHR participants met criteria for an anxiety disorder but anxiety disorders did not predict transition to psychosis.

Mood disorders have been proven to be predictors of conversion. In an EPOS study, bipolar and depressive disorders were shown to predict conversion to psychosis over anxiety disorders (Salokangas et al., 2012).

Specifically, with cannabis use, the research findings on the association between use and transition to psychosis have been inconsistent. Phillips and colleagues did not find that cannabis use or dependence impacted transition to psychosis (Phillips et al., 2002). Similarly, another study, conducted by Buchy and colleagues with a sample of 170 CHR subjects found that cannabis use did not predict later conversion to psychosis (Buchy et al., 2014). Additionally, low to moderate lifetime cannabis was found not to predict transition to psychosis in another sample (Auther et al., 2012). Yung et al., 2004 also did not find an association between conversion to psychosis and cannabis abuse. Auther et al. (2015) also found that cannabis use and abuse were not predictive of conversion

Other studies have found a link between cannabis use and transition to psychosis. One study found that age of onset of cannabis use was associated with onset of high-risk symptoms suggesting that cannabis use may play a role in the development of psychosis (Dragt et al., 2012). Similarly, another study found that early onset of cannabis use (before age 15), frequency of use, and continued use were associated with transition to psychosis (Valmaggia et al., 2014).

Regarding other substances, there are mixed findings on the association between nicotine use and conversion. Kristensen & Cadenshead (2007) observed a line between nicotine use and conversion. In this same study, among the 6 participants who converted to psychosis, 4 of them smoked cigarettes. Similarly, Weiser et al. (2004) observed that the risk for schizophrenia was higher in adolescents who smoked at least one cigarette a day. Additionally, there was a significant association between the number of cigarettes smoked and the risk for psychosis as higher nicotine use was associated with higher- risk for psychosis. However, Zammit et al. (2003) found low rates of transition to psychosis among cigarette smokers

Course of Axis I and Axis II Disorders

Although the above studies have been instrumental in providing information about the occurrence of Axis I disorders in high-risk individuals, less is known about how these disorders impact long-term outcomes. Some studies that have attempted to address this issue through longitudinal studies. McAusland and colleagues (2017) found that 51% of their sample met criteria at the 24-month follow up for anxiety disorder with several participants presenting with more than one anxiety disorder.

Lin et al. (2015) investigated the comorbidity rates of nonpsychotic diagnoses in high-risk individuals at the 12-month follow-up and found high prevalence rates of depressive and anxiety disorders at follow-up of 48.7% and 34.5% respectively. Participants meeting criteria for more than one disorder at follow-up presented with more severe symptoms, higher distress, and lower functioning. In their study, 68.1 % of their at- risk participants met diagnostic criteria for at least one Axis I disorder at the 7-year follow-up period with mood disorders (48.7%), anxiety disorders (34.5%), and substance use disorders (29.2%) being the most common. In this sample, comorbid mental disorders had the tendency to persist or recur (51.6% persistent/recurring vs. 26.0% remittent course). Specifically, mood disorders (38.4%) and then followed by anxiety disorders (16.2%) were the most persistent /recurrent disorders. Incident diagnoses developed in 37.5% of participants and 7.3% had no diagnoses. Comorbid disorders were associated with lower GAF scores at one-year follow-up. These findings suggest that Axis I disorders tend to persist over time and are correlated with functioning deficiencies. This dissertation study will follow the methodological approach described by Lin et al. (2015) to explore the developmental course of psychiatric disorders in the RAP sample.

We expect to have similar findings with anxiety and mood disorders being the most persistent and recurrent in this study. We will further expand on Lin et al and colleagues' study by also assessing the progression of psychiatric disorders using the clinical staging RAP model and comparing progression of disorders in the RAP subgroups. Additionally, we added attention-deficit and disruptive behavior disorders and personality disorders to our analyses to explore the progression of these disorders.

Aims and Hypotheses

Aim 1: Examine the baseline prevalence rates of psychiatric disorders in the sample of CHR participants (CHR + and CHR- groups) in the RAP Program. This study will determine if there are differential rates of psychiatric disorders between the RAP prodromal groups (CHR-, CHR+) compared to each other. This study will also assess the relationship between psychiatric disorders and attenuated symptoms and functioning.

Aim 2: Examine the long-term stability of psychiatric disorders in CHR participants in the RAP Program. Determine if there are differential rates of stability (persistent/recurrent, remitted, incident, and never present) of psychiatric disorders for the RAP high-risk groups (CHR-, CHR+).

Aim 3: Identify whether positive symptoms predict conversion over and above Axis I disorders.

Hypotheses for Aim 1

Hypothesis 1: There will be no differences in rates of comorbid psychiatric disorders between the RAP prodromal groups (CHR- and CHR+).

Hypothesis 2: Comorbid psychiatric disorders will be related to higher attenuated positive and negative symptoms, poorer social/role functioning scores at baseline.

Hypothesis for Aim 2

Hypothesis 3: In comparison to other psychiatric disorders, mood and anxiety disorders will be persistent/recurrent from baseline to last follow-up for both high-risk subgroups.

Hypothesis for Aim 3

Hypothesis 4: Attenuated positive symptoms will be a significant predictor of conversion to psychosis over and above Axis I disorders at baseline. Additionally, of all the Axis I disorders, mood disorders at baseline will be the strongest predictor of conversion.

Chapter 3: Methods

Ethics in Research

This study used previously collected data by the Recognition and Prevention (RAP) Program and was therefore determined to be exempt by St. John's University's Institutional Review Board (IRB: #1118 143), which reviews all research for compliance with ethical guidelines. Researcher was also granted permission to use data for dissertation by P.I. Dr. Barbara A. Cornblatt, Ph.D., M.B.A.

Participants

Participants were 156 (110 males and 46 females) who participated in the Recognition & Prevention (RAP) Program during Phase I (2000-2006). The RAP Program has been continuously funded by the National Institute of Mental Health (NIMH) since 2000. It is located at The Zucker Hillside Hospital (ZHH) which is part of the Northwell Health hospital system in New York. The RAP Program conducts research and provides interventions for adolescents and young adults who present in the prodromal or high-risk stage of psychotic illness.

All participants were help-seeking individuals referred from health care providers in the inpatient and outpatient psychiatry departments at ZHH, from private practitioners in the community, or were self-referred. Participants between the ages of 12-22 years of age were recruited for this study if they met criteria for one of the CHR categories: Clinical High Risk Negative (CHR-) and Clinical High Risk Positive (CHR+). High risk participants were included in the RAP Program research based on the presence of attenuated positive and negative symptoms as assessed by the SOPS measure. Participants with at least one attenuated negative symptom at a moderate (score of 3) or

higher level, but with no attenuated positive symptoms, were classified as Clinical High Risk – Negative (CHR -). Participants with at least one attenuated positive symptom in the moderate (score of 3) to severe (score of 5) range were classified as Clinical High Risk – Positive (CHR+). The final category of the RAP model is the Schizophrenia-like Psychosis (SLP) group, defined as a person who has a positive symptom that has reached a psychotic level (score of 6). This is thought to be an intermediate stage between the prodrome (CHR- and CHR+ groups) and a full diagnosis of schizophrenia. Please see Figure 2. Note that in this dissertation, the SLP group will not be used.

Participants were excluded from the study if they met criteria at baseline for a diagnosis of a schizophrenia-spectrum disorder (i.e. schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder), a mood disorder with psychotic features, or a bipolar spectrum disorder. Participants were also excluded if they had lack of English fluency, an estimated IQ <70, or a diagnosis of a medical or neurological disorder known to affect the developing brain.

Procedures

Participants who met criteria for the study were informed of the research protocol, given the opportunity to ask questions, and were invited to participate in the study. Written informed consent was obtained from participants 18 years of age and older or from a parent or guardian if participant was under the age of 18 (in addition to written assent). Participants were informed that their participation in the study was voluntary and that they could withdraw from the study at any time.

For this study, confidentiality was maintained by the assignment of subject numbers to participants in the study. Data collected from participants were kept in

locked file cabinets at Zucker Hillside Hospital. Risks associated with participation in this study include possible fatigue or discomfort when responding to questions especially over a lengthy period of time. Benefits of participation in this research include identification of disorders that may be impacting the individual's functioning. This information could also be used to help the individual secure a referral for treatment. Other benefits include advancing our knowledge and understanding of individuals who are at-risk for psychosis with the hope of identifying effective forms of treatment. All procedures were approved by the IRB at Northwell Health.

Testing procedures consisted of a battery of clinical, behavioral, functional, and neurocognitive measures taking approximately 3.5 hours that were collected at baseline and approximately every 6 months for up to 5 years. Average length of follow-up is 2.9 years and therefore had varying follow-up times. Participants were compensated $10 an hour for their time and effort while participating in the research procedures. For the purposes of this dissertation, only data concerning prodromal symptoms, Axis I and Axis II disorders, and social and role functioning obtained via structured clinical interviews will be analyzed.

Generally, parents/guardians were interviewed before the participant as they could provide useful information that could be used when interviewing participants. After interviewing the parent/guardian, the assessor interviewed the participants, noting and reconciling any discrepancies in the reports. Assessors were all at the master's level or above and were trained in administration and scoring of all the measures. Once completed, interviews were then scored by the interviewer and presented to an expert diagnostician at a consensus meeting.

Measures

Demographic Variables. Age, sex, and US census-based race and ethnicity categories were obtained for each participant. Subjects and their guardians provided demographic information regarding age, sex, racial/ethnic identification, education, and annual household income. The instruments show good face validity and are typical of those used for research in hospital settings. Estimated IQ was obtained by administering the Vocabulary and Block Design subtests from the Wechsler Intelligence Scale for Children-Third Edition (WISC-III; Wechsler, 1991) and the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1981) depending on the age of the participant.

Assessment of High-Risk Symptoms. The (SOPS) and its companion Structured Interview for Prodromal Symptoms or (SIPS) were developed by McGlashan and colleagues to assess symptoms for identifying prodromal states (McGlashan et al., 2010). The SOPS contains five items measuring positive symptoms (unusual thought content, suspiciousness, grandiosity, perceptual abnormalities, speech disorganization), six items measuring negative symptoms (social isolation, avolition, decreased expression of emotion, decreased experience of emotion, decreased ideational richness, decreased role functioning), four items measuring disorganization symptoms (odd appearance, bizarre thinking, poor focus/attention, poor hygiene), and four items measuring general symptoms (sleep disturbance, dysphoric mood, motor disturbance, decreased stress tolerance). These symptoms are rated on a 7-point anchored scale ranging from 0 (not present) to 6 (psychotic or extreme intensity). According to Miller et al (2003), the SOPS has good internal consistency with a Cronbach alpha coefficients above 0.75 for all subscales.

The Schedule for Affective Disorders and Schizophrenia for School-Age Children, Epidemiologic Version. The K-SADS-E is a semi-structured interview that uses both child and parent interviews to diagnostically assess current and lifetime disorders such as affective, anxiety, behavioral, psychotic disorders, and substance use disorders **(**K-SADS-E; Orvaschel & Puig-Antich, 1994). Current episodes are rated on a severity scale and identified as mild, moderate, or severe and past episodes are rated as absent or present. Ratings are based on specific DSM-IV criteria for each disorder assessed (Ambrosini et al., 2000). The KSADS-E has been found to have good internal consistency of its scales, with reported Cronbach alpha coefficients between .51 and .75 for its subscales (Ambrosini et al., 2000).

The Structured Interview for the Diagnosis of Personality for DSM- IV. The SIDP-IV assessed personality traits/disorders (SIDP-IV; Pfohl, Blum, &Zimmerman, 1995). This semi-structured interview assesses the diagnostic criteria for the 10 personality disorders in the *DSM-IV* (i.e. paranoid, schizoid, schizotypal, borderline, narcissistic, histrionic, antisocial, avoidant, dependent, and obsessive-compulsive). Questions are arranged by themes instead of by disorders (e.g. interpersonal relationships, emotions, interests) and each criterion is rated on a scale from 0 to 3. Each item represents a specific symptom or trait associated with a disorder and is rated as 0 (not present or limited to rare isolated examples), 1 (subthreshold-some evidence of the trait but is not sufficiently pervasive or severe to consider the criterion present), 2 (present-criterion is clearly present (at least 50% of the time) for most of the last 2 years), or 3 (strongly present- criterion is associated with subjective distress or some impairment in social or occupational functioning or intimate relationships.) In order to receive a

diagnosis for a personality disorder, the participant must meet the required number of symptoms for that particular personality disorder at either the "present" or "strongly present" level. The SIDP-IV has good internal consistency, with a Cronbach alpha coefficient of at least 0.70 for it's scales (Jane et al., 2006).

Global Functioning: Social (GF:Social) and Role (GF:Role) scales. Social and role functioning were assessed using these measures. These scales account for age and phase of illness and detect functional changes over time. Unlike other scales, these scales avoid confounding functioning with psychiatric symptoms. The GF: Social scale assesses peer relationships, peer conflict, age-appropriate intimate relationships, and involvement with family members. The GF: Role scale rates performance level and amount of support needed in one's specific role (i.e., school or work). For both scales, scores range from 1 (extreme dysfunction) to 10 (superior functioning) and anchors are provided at each increment. Ratings for each of the scales were obtained from clinical information based on clinician reports and interviews (Cornblatt et al., 2007). The Global Functioning: Social (GF:Social) and Role (GF:Role) scales have excellent internal consistency with a Cronbach's alpha coefficient of above 0.80 for both scales (Cornblatt et al., 2007).

Research design and analysis. All statistical procedures were calculated using SPSS version 22.

Missing data. Before performing any analyses, the categorical and continuous variables were checked for any errors that may fall outside of the possible range of values, as this may distort future analyses and were also checked for missing values. Data were missing for NAPLS IQ (7.7%) and for Sum total of negative symptoms (13.5%). It was determined that the data was missing completely at random and expectation

maximization was imputed to assign missing values (Dempster, Laird, N., & Rubin, 1977).

Preliminary analysis. Descriptive statistics were calculated for basic demographic comparisons on gender, age, IQ, and race between RAP subgroups (CHR-, CHR+). Chi squares were computed for categorical variables (gender and race) and ANOVAs for continuous variables (age and IQ).

Statistical Analyses. Axis I disorders will be analyzed individually and collapsed into the following summary categories: mood disorders, anxiety disorders, substance use disorders, and other disorders. Axis II disorders will be collapsed into 3 clusters (Cluster A, Cluster B, Cluster C) in addition to being examined as individual personality disorders (10 disorders).

For Hypothesis 1, Chi-square analyses will be used to compare the prevalence rates for the above-mentioned groupings of Axis I and Axis II disorders at baseline between the prodromal groups (CHR- and CHR+; Hypothesis 1).

For Hypothesis 2, the association between psychiatric disorders (mood, anxiety, substance use, and attention-deficit and disruptive behavior disorders), functioning (social and role functioning), and attenuated symptoms (positive and negative symptoms) will be tested by evaluating correlations between these variables for CHR- and CHR+ groups separately. If significant correlations are found between the variables, then this will be followed up with ANOVAs to determine if there are differences in functioning (social or role functioning) based on psychiatric disorders and by group status (CHR+/CHR-). For these analyses, independent variables (psychiatric disorders and CHR group status) and dependent variables (social/role functioning, attenuated symptoms) will

be entered into the models to determine if there are significant differences in functioning and attenuated symptom presentation based on type of psychiatric disorder and CHR group status. To reduce Type 1 Error, the critical *p* value will be adjusted to account for multiple comparisons ($p < 0.01$).

For Hypothesis 3, we will evaluate the stability of Axis I and II disorders, by following the methodological approach illustrated by Lin et al. (2015). To examine the course of the Axis I and II disorders, participants will be organized into four different categories. If the disorder was not present at baseline and follow-up, it will be categorized as "not present." If the disorder was present at baseline and follow-up, it will be classified as "persistent/recurrent". Disorders that were present at baseline but absent at follow-up will be labeled "remitted" and disorders that were present at follow-up but absent at baseline will be classified as "incident" cases. The frequencies of each category will be obtained for CHR- and CHR+ groups separately and compared by psychiatric disorders.

For Hypothesis 4, we will assess predictors of conversion by first examining the association between conversion and the SOPS scale (positive symptoms, negative symptoms, disorganized symptoms, and general symptoms) by calculating correlation coefficients. The coefficients found to be significant at the $p<.01$ level would then be entered into the binary logistic regression model in conjunction with Axis I disorders (mood, anxiety, substance use, attention-deficit and disruptive behavior disorders) to identify predictors of conversion.

Chapter 4: Results

This chapter offers an overview of the results of preliminary analyses such as descriptive statistics of the CHR+ and CHR- groups. It also reports the findings of chi-square analyses, ANOVAs, and regression analyses used to analyze clinical and functional outcomes for the two high-risk groups.

Demographics and Clinical Characteristics

Demographic and clinical characteristic information for the CHR subgroups are presented in Tables 1.1, 1.2. There were one hundred and fifty-six participants in this sample (110 males and 46 females). Frequencies were obtained assessing group differences based on gender and ethnicity. Results indicated that males were a larger proportion of this sample (70.5%) compared to females (29.5%). When considering CHR group status for demographics, the CHR+ subgroup consisted of 65 males (64.4%) and 36 females (35.6%). In the CHR- group, 45 participants identified as male (81.8%) and 10 (18.2%) identified as female. Significant differences on gender were found at the .05 level F (1,154)=5.334, p= .022. In terms of ethnicity, participants described themselves as mostly White (n = 122, 78.2%), Black (n =14, 9.0%), Asian (n =14, 9.0%), and Other/Mixed (n =6, 3.8%) and there were no significant differences found for ethnicity.

ANOVAS were performed to compare the differences in age, IQ, total positive symptoms, total negative symptoms, total disorganized symptoms, total generalized symptoms, social functioning, and role functioning between the high-risk groups. Participants were between the ages of 12 and 22 (M = 15.97, SD = 2.14). No significant

differences were found for age F (1,154)=.589, p= .444 or IQ F (1,142) = .224, p =.637 between the CHR subgroups.

Participants completed the SOPS which measured total positive, negative, disorganized, and general symptoms. Generally, there was a trend of CHR+ participants scoring higher compared to CHR- participants on these scales. Significant differences were found for the report of positive F (1,154)=150.482, p=.000 and negative symptoms F (1,154)=8.659, p= .004. These results are expected given that assignment to the CHR groups are based on the presence of attenuated positive and negative symptoms. There were also significant differences in the report of disorganized symptoms at the .05 level F (1,154)=.414, p= .004.

In assessing functioning between the two RAP subgroups, significant differences were found for social functioning F (1,154)=7.991, p=.005 but not for role functioning F(1,154) =.320, p = 573.

Table 1.1

Demographics for Entire Sample

	Frequency (*n*)	Percentage (%)
Gender		
Male	110	70.5
Female	46	29.5
Ethnicity		
White	122	78.2
Black	14	9.0
Asian	14	9.0
Other/Mixed	6	3.8

Table 1.2

Descriptive Statistics for High-Risk groups

	CHR+ N=101	CHR- N=55	*F*	*p*
Age	16.07 ± 2.17	15.79 ± 2.09	.589	.444
Gender, N(%)			5.334	**.022***
Female	36 (35.6%)	10 (18.2%)		
Male	65 (64.4%)	45 (81.8%)		
Ethnicity, N (%)			3.410	.067
Caucasian	81 (80.2%)	41 (74.5%)		
Black	11 (10.9%)	3 (5.5%)		
Asian	7 (6.9%)	7 (12.7%)		
Other/Mixed	2 (2.0%)	4 (7.3%)		
IQ	102.85 ± 15.70	103.97 ± 15.79	.181	.671
SOPS Total Positive	8.85 ± 3.85	1.98 ± 2.09	150.482	**.000****
SOPS Total Negative	12.83 ± 5.42	15.55 ± 5.70	8.659	**.004****
SOPS Total Disorganized	5.78 ±3.50	4.42 ± 3.51	5.414	**.021***
SOPS Total General	8.49 ±3.87	4.42 ± 3.51	2.209	.139
Social Functioning	6.03±1.43	5.40± 1.12	7.991	**.005****
Role Functioning	5.55±2.03	5.35± 2.50	.320	.573

**p is significant at the 0.01 level
*p is significant at the 0.05 level

Hypothesis 1

Chi-square tests of independence were used to compare the prevalence rates of psychiatric disorders between the high-risk groups (CHR- and CHR+) at baseline. To perform these analyses, Axis I disorders were collapsed into the following categories: mood disorders, anxiety disorders, substance use disorders, and attention-deficit and disruptive behavior disorders. Personality disorders were collapsed into 3 clusters (Cluster A, Cluster B, Cluster C) in addition to being examined as individual personality disorders (paranoid, schizoid, schizotypal, antisocial, borderline, histrionic, narcissistic, avoidant, dependent, and obsessive compulsive).

Chi-square analyses were performed to assess the relationship between high-risk status (CHR + and CHR-) and mood disorders, anxiety disorders, substance use disorders, attention-deficit and disruptive behavior disorders, and personality disorders. The Fisher's exact test was used to determine associations between the variables as one or more expected cell counts in the crosstabulations were less than five (Sprent et al., 2011). As displayed in Table 2.1, chi-square analyses revealed no significant differences in the proportion of high-risk participants who report mood, anxiety, substance use disorders, at baseline. As seen in Table 2.2, significant differences were found in participants who met criteria for paranoid personality disorder x^2 (1, n=155) = 6.954, p =.008, schizoid personality disorder x^2 (1, n =155)= 7.650, p=.006, and borderline personality x^2 (1, n= 155)= 6.330, p=.009. CHR- participants were more likely to endorse schizoid personality disorder and CHR+ participants were more likely to report paranoid personality disorder and borderline personality disorder.

As seen in Table 2.1, a large proportion of CHR+ and CHR- participants reported mood or anxiety disorders at baseline, 79.2% and 78.2 respectively. Additionally, when diagnoses are examined separately, 62.4% of CHR+ participants and 54.5% of CHR- participants met criteria for a mood disorder at baseline. Likewise, 54.5% of CHR+ participants and 45.5% of CHR- participants reported an anxiety disorder at baseline. Lowest proportions among high-risk participants were reported for substance use, 8.9% for CHR+ and 3.6% for CHR- participants. ADHD disorders were endorsed by CHR participants, with 33.7% in the CHR+ subgroup and 25.5% in the CHR-group. As for personality disorders, which are displayed in Table 2.2, 45.5% of CHR+ and 51.9% of CHR- participants did not meet criteria for an Axis II disorder. Among CHR- participants there was also a similarity in presentation of Cluster A and C personality disorders (22.2%). Generally, a larger proportion of CHR+ participants endorsed personality disorders compared to CHR- participants.

The results indicate that there are differences in Axis II presentation, therefore partially supporting Hypothesis I. This further supports monitoring symptoms over time to distinguish between the RAP subgroups.

Table 2.1

Prevalence Rates of Axis I Disorders at Baseline

	CHR + (%) N=161	CHR- (%) N=55	χ^2	Fisher exact *p*-value
No Axis I Disorder	3(3.0)	4(7.3)	1.538	.243
		Mood and Anxiety Disorders		
Any Mood Disorder	63 (62.4)	30 (54.5)	.907	.341
Major Depressive Disorder	44 (43.6)	16 (21.2)	3.152	.087
Dysthymic Disorder	6 (5.9)	4 (7.3)	.105	.742
Bipolar Spectrum Disorder[a]	0 (0.0)	0 (0.0)	-	-
Other mood Disorder	14 (13.9)	10 (18.2)	.511	.493
Any Anxiety Disorder	55 (54.5)	25 (45.5)	1.155	.317
Agoraphobia	2 (2.0)	0 (0.0)	1.103	.541
GAD	12 (10.4)	4 (7.3)	.822	.422
OCD	9 (8.9)	3 (5.5)	.599	.542
Panic Disorder	8 (7.9)	0 (0.0)	4.592	.051
PTSD	3 (3.0)	1 (1.8)	.189	1.000
Social Phobia	23 (22.8)	19 (34.5)	2.509	.132
Specific Phobia	9 (8.9)	4 (7.3)	.125	1.000
Other Anxiety Disorder	13 (12.9)	2 (3.6)	3.494	.087
Any mood or anxiety Disorder	80(79.2)	43 (78.2)	.022	1.000
		Substance Disorders		
Any substance Disorder	9 (8.9)	2 (3.6)	1.512	.330
Alcohol Disorder	2 (2.0)	0 (0.0)	1.103	.541
Cannabis Disorder	7 (6.9)	2 (3.6)	.711	.494
Cocaine Disorder	1 (1.0)	0 (0.0)	.548	1.000
Hallucinogen Disorder	0 (0.0)	1 (1.8)	1.848	.353
Nicotine Disorder	1 (1.0)	0 (0.0)	.548	1.000
Polysubstance use Disorder	1 (1.0)	0 (0.0)	.548	.461
		Other Disorders		
ADHD	34(33.7)	14(25.5)	1.126	.289
Conduct Disorder	3(3.0)	2 (3.6)	.051	.821
Disruptive Behavioral Disorder NOS	1(1.0)	0 (0)	.548	.459
Oppositional Defiant Disorder	31(30.7)	9 (16.4)	3.835	.050
Adjustment Disorder	3 (3.0)	3 (5.5)	.594	.441
Intermittent Explosive Disorder	1 (1.0)	1 (1.8)	.193	.660
Learning Disorder	5 (5.0)	5 (9.1)	1.018	.313
Developmental Disorder	5 (5.0)	3 (5.5)	.019	.892
Tic Disorder	1 (1.0)	1(1.8)	.193	.660

[a] No participants reported Bipolar Spectrum Disorder at baseline
[**] *p* is significant at the .01 level

Table 2.2

Prevalence Rates of Axis II Disorders at Baseline

	CHR+ (%) N=101	CHR- (%) N=55	χ^2	Fisher exact *p*-value
No Axis II disorder	46 (45.5)	28 (51.9)	.561	.502
Cluster A	25 (24.8)	12(22.2)	.124	.844
Paranoid PD	12 (11.9)	0 (0.0)	6.954	**.009****
Schizoid PD	7 (6.9)	12 (22.2)	7.650	**.009****
Schizotypal PD	11 (10.9)	1 (1.9)	4.025	.058
Cluster B	11(10.9)	1(1.9)	4.025	.058
Antisocial PD[a]	0 (0.0)	0 (0.0)	-	-
Borderline PD	11 (10.9)	0 (0.0)	6.330	**.009****
Histrionic PD[b]	0 (0.0)	0 (0.0)	-	-
Narcissistic PD	0 (0.0)	1(1.9)	.102	.348
Cluster C	32 (31.7)	12(22.2)	1.549	.263
Avoidant PD	29 (28.7)	12 (22.2)	.762	.447
Dependent PD	2 (2.0)	0 (0.0)	1.083	.543
Obsessive Compulsive PD	3(3.0)	0(0.0)	1.636	.552

[a] No participants reported Histrionic PD diagnoses at baseline
[b] No participants reported Antisocial PD diagnoses at baseline
**p is significant at the 0.01 level

Hypothesis 2

Correlation analyses and ANOVAS were conducted to determine if there are differences in functioning or attenuated symptom presentation by psychiatric disorder and CHR group status. Point biserial correlation coefficients were first performed to determine the relationships between psychiatric disorders, attenuated positive/negative symptoms, and social/role functioning for each of the high-risk groups (CHR+ and CHR-). For the CHR+ subgroup, moderate correlations were found between Cluster A Personality Disorder and total positive symptoms (*r = .268, n=101, p< .01)*, total negative symptoms (*r = .330, n = 101, p<.01*), and social functioning (*r = -.318, n= 101, p <.01)*. For the CHR- subgroup, there was a moderate positive correlation between

Cluster A personality disorder and total negative symptoms (*r=.378, n=54, p<.001*) and a strong negative correlation with social functioning (*r=-.557, n=54, p<.001*). There was also a moderate, negative correlation between mood and role functioning (*r= -.404, n= 55, p<.01*).

For the CHR+ subgroup there were a few other significant correlations that were obtained at the *p<.01* level although not part of our research aims such as cluster C and anxiety (*r=.452, n =101, p<.01*), social functioning and total negative symptoms (*r=-.501, n=101, p<.01*), role functioning and total negative symptoms (*r=-.439, n=101, p<.01).* For the CHR- subgroup there were moderate to strong correlations obtained between Cluster C and anxiety (*r=.576, n=54, p<.01*) and role functioning and total negative symptoms (*r=-.416, n=54, p<.01*).

Although these analyses are only focusing on significant correlations at the .01 level, it is noteworthy that there are several significant correlations at the .05 level for CHR+ participants. These include small correlations between mood disorders and Cluster B personality disorders (*r=.206, n=101, p<.01*) and substance disorders and social functioning (*r=.237, n=101, p<.01*). Small, negative correlations were found between anxiety and attention-deficit and disruptive behavior disorders (*r=-.202, n=101, p<.01*), Cluster A personality disorders and role functioning (*r=.203, n=101, p<.01*), and Cluster C personality disorder and social functioning (*r=-.253, n=101, p<*.01). See Tables 3.1, 3.2.

Overall, it appears that there are similarities in the presentation of Cluster A personality disorder among the CHR subgroups with significant associations between total negative and social functioning for both CHR+ and CHR- participants. Additionally,

significant associations were found between Cluster A personality disorder and total positive symptoms for the CHR+ subgroup and between mood disorder and role functioning.

After determining significant associations between attenuated positive and negative symptoms and functioning for Cluster A personality disorders and mood disorders, additional analyses were conducted using ANOVAS to further explore if there are differences in functioning or attenuated symptoms by disorder (Cluster A personality disorder or mood disorder) or by CHR group status (CHR+, CHR-). These results confirmed that role functioning has an impact on mood disorders F (1,53)=10.337, p=.002 for the CHR-subgroup. Additionally, these follow-up analyses confirmed that attenuated positive symptoms F (1,99)=7.632, p=.007, negative symptoms F(1,99)=12.060, p=.000, and social functioning F (1,99)=11.136, p=.001 have an impact on Cluster A personality disorders for the CHR+ subgroup. Similarly, for the CHR-subgroup attenuated negative symptoms F (1,53)= 8.674 p=.005 and social functioning F (1,53)=23.424, p=.000 were found to also have an impact on Cluster A personality disorder presentation.

These results partially support our hypothesis, as mood disorders were associated with lower role functioning and Cluster A personality disorders were associated with lower social functioning and attenuated negative symptoms.

Table 3.1

Correlation Matrix for Clinical and Functional Characteristics in CHR + subgroup

	M	A	S	B.	CA	CB	CC	Pos	Neg	Soc	Role
Mood	---										
Anxiety	.152	---									
Substance	.099	-.063	---								
Behavioral	-.064	-.202*	.065	---							
Cluster A PD	.019	-.074	-.099	-.144	---						
Cluster B PD	.206*	.192	.114	-.077	.020	---					
Cluster C PD	.177	**.452****	-.064	-.131	.152	.172	---				
Total Pos	-.057	.125	-.024	-.107	**.268****	.188	.176	---			
Total Neg	.114	-.013	.032	-.004	**.330****	-.045	.160	.046	---		
Social Func	.002	-.121	.237*	-.024	**-.318****	.015	-.253*	-.086	**-.501****	---	
Role Func	.011	.054	-.137	-.154	-.203*	-.064	-.081	-.056	**-.439****	.187	---

**Correlation coefficient is significant at the 0.01 level

*Correlation is significant at the 0.05 level

Table 3.2

Correlation Matrix for Clinical and Functional Characteristics in CHR - subgroup

	M	A	S	B	CA	CB	CC	Pos	Neg	Soc	Role
Mood	---										
Anxiety	-.120	---									
Substance	-.213	.018	---								
Behavioral	.100	-.247	.018	---							
Cluster A PD	-.060	-.228	-.105	-.050	---						
Cluster B PD	.123	-.128	-.027	-.128	-.073	---					
Cluster C PD	.030	**.576****	-.105	-.050	-.071	-.073	---				
Total Pos	.133	-.080	-.045	.043	.041	.207	.150	---			
Total Neg	.257	-.052	-.043	-.104	**.378****	.007	-.003	.433	---		
Social Func	.066	-.165	.018	.132	**-.557****	-.176	-.052	.051	**-.453****	---	
Role Func	**-.404****	.035	.130	-.187	.004	-.128	.112	-.102	**-.416****	-.090	---

**Correlation coefficient is significant at the 0.01 level

*Correlation is significant at the 0.05 level

Table 3.3

Association between Mood Disorders and High-Risk Symptoms and Functioning

Predictor	*df*	*F*	*sig*
CHR+			
Total Positive	(1,99)	.320	.573
Total Negative	(1,99)	1.299	.257
Social Functioning	(1,99)	.000	.985
Role Functioning	(1,99)	.012	.915
CHR-			
Total Positive	(1,53)	.959	.332
Total Negative	(1,53)	3.733	.059
Social Functioning	(1,53)	.232	.632
Role Functioning	(1,53)	10.337	**.002****

**p is significant at the 0.01 level

Table 3.4

Association between Cluster A Personality Disorders and High-Risk Symptoms and Functioning

Predictor	*df*	*F*	*sig*
CHR+			
Total Positive	(1,99)	7.632	.007**
Total Negative	(1,99)	12.060	.000**
Social Functioning	(1,99)	11.136	.001**
Role Functioning	(1,99)	4.240	.042
CHR-			
Total Positive	(1,53)	.088	.768
Total Negative	(1,53)	8.674	.005**
Social Functioning	(1,53)	23.424	.000**
Role Functioning	(1,53)	.001	.977

**p is significant at the 0.01 level

Hypothesis 3

Table 4.1 displays the course of psychiatric disorders for high- risk groups by presenting frequencies of baseline, remission, incidence, persistence/recurrence, and absence of Axis I and Axis II disorders. As seen in Table 4.1, all high-risk participants, had a disorder present at baseline. For CHR+ participants, 34.5% had a disorder that remitted, and 75.9% had a disorder that was persistent, and 44.8% had a new onset of a disorder. As observed in CHR- participants, 38.5% had a disorder that remitted, 100% had a disorder that was persistent/recurrent, and 23.1% had a new onset of a disorder.

Mood disorders. 58.6% of CHR+ participants had a mood disorder at baseline, 10.3% had a mood disorder that remitted and 48.3% had a mood disorder that was persistent. 31.0% of CHR+ participants never had a mood disorder and 10.3% developed a mood disorder. For CHR- participants, 30.8% had a mood disorder present at baseline, 23.1% had a mood disorder that was persistent, developed, or never present.

Anxiety disorders. For those participants with anxiety disorders, 44.8% of CHR+ participants reported an anxiety disorder at baseline, 6.9% developed an anxiety disorder and 48.3% never had an anxiety disorder. In comparison, for CHR- participants, 53.8% had an anxiety disorder at baseline, 7.7% had an anxiety disorder that remitted, 46.2% had an anxiety disorder that was persistent and never had an anxiety disorder.

Substance Use. For substance use, 6.9% of CHR+ and 15.4% of CHR- participants had a substance use disorder that was present at baseline. 6.9% of CHR+ participants had a substance use disorder that remitted, 0% had a substance use disorder that was persistent, 93.1% of participants never had a substance use disorder and 3.4% developed a substance use disorder. For CHR- participants, 0% had a substance use

disorder that remitted or developed, 15.4% had a substance use disorder that was persistent, 84.6% never had a substance use disorder. Also, substance use disorders were more likely to be never present at baseline or follow-up.

Personality disorders. Of all CHR+ participants, 44.8% of participants had a personality disorder present at baseline, 10.3% had a personality disorder that remitted, 61.5% had a personality disorder that was persistent, 13.8% developed a personality disorder and 41.4% never had a personality disorder. In comparison, 61.5% of CHR- participants had a personality disorder at baseline, 7.7% had a personality disorder that remitted, 61.5% had a personality disorder that was persistent/recurrent, 0% developed a personality disorder, and 30.8% never had a personality disorder.

Attention-deficit and disruptive behavior disorders. Of all high-risk participants, 51.7% of CHR+ subjects and 30.8% of CHR- subjects had an attention-deficit and disruptive behavior disorder present at baseline. For CHR+ participants, 17.2% had an attention-deficit and disruptive behavior disorder that remitted, and 34.5% had disorders that were persistent, 3.4% developed one of these types of disorders, and for 37.9% of participants, attention-deficit and disruptive behavior disorders were not present at baseline or follow-up.

Additionally, high-risk participants developed psychotic disorders at similar rates, with 20.7% of CHR+ participants and 23.1% of CHR- participants reporting psychosis at follow-up.

It was hypothesized that mood and anxiety disorders would be the most persistent/recurrent but our analyses revealed that these disorders in addition to personality disorders and attention-deficit and disruptive behavior disorders were also

persistent, therefore rejecting our hypothesis. It is noteworthy that for CHR- participants, all disorders at baseline were persistent/recurrent.

Table 4.1

The course of Axis I and Axis II Disorders

Status of Disorder	CHR + (N=29, %)	CHR- (N=13, %)
Present at baseline		
Any disorder	29 (100.0)	13 (100.0)
Any mood disorder	17 (58.6)	4 (30.8)
Any anxiety disorder	13 (44.8)	7 (53.8)
Any substance use disorder	2 (6.9)	2 (15.4)
Any personality disorder	13 (44.8)	8 (61.5)
Any attention-deficit and disruptive behavior disorder	15 (51.7)	4 (30.8)
Remitted		
Any disorder	10 (34.5)	5 (38.5)
Any mood disorder	3 (10.3)	2 (15.4)
Any anxiety disorder	3 (10.3)	1 (7.7)
Any substance use disorder	2 (6.9)	0 (0.0)
Any personality disorder	3 (10.3)	1 (7.7)
Any attention-deficit and disruptive behavior disorder	5 (17.2)	1 (7.7)
Incident		
Any disorder	13 (44.8)	3 (23.1)
Any mood disorder	3 (10.3)	3 (23.1)
Any anxiety disorder	2 (6.9)	0 (0.0)
Any substance use disorder	1 (3.4)	0 (0.0)
Any personality disorder	4 (13.8)	0 (0.0)
Any attention-deficit and disruptive behavior disorder	1 (3.4)	0 (0.0)
Any Psychotic disorder	6 (20.7)	3 (23.1)
Persistent or Recurrent		
Any disorder	22 (75.9)	13 (100.0)
Any mood disorder	14 (48.3)	3 (23.1)
Any anxiety disorder	10 (34.5)	6 (46.2)
Any substance use disorder	0 (0.0)	2 (15.4)
Any personality disorder	10 (34.5)	8 (61.5)
Any attention-deficit and disruptive behavior disorder	10 (34.5)	3 (23.1)
Never present		
Any disorder	0 (0.0)	0 (0.0)
Any mood disorder	9 (31.0)	7 (53.8)
Any anxiety disorder	14 (48.3)	6 (46.2)
Any substance use disorder	27 (93.1)	11(84.6)
Any personality disorder	12 (41.4)	4 (30.8)
Any attention-deficit and disruptive behavior disorder	11 (37.9)	9 (69.2)

N=42

Hypothesis 4

Correlation analyses were performed to evaluate the association between conversion and types of symptoms, revealing positive associations between total positive symptoms on the SIPS and conversion (r =.26, p< *.001).* See Table 5.1.

A binary logistic regression was performed to assess the impact of a number of factors on the likelihood that participants would convert to psychosis. First data were checked to ensure that none of the assumptions were violated (sample size, multicollinearity, and outliers). Independent variables for the model included positive symptoms, Axis I disorders(baseline mood, baseline anxiety, baseline substance use and baseline attention-deficit and disruptive behavior disorders). The full model containing all the predictors was statistically significant, χ^2 (5, N=101)=14.92, p <.05, indicating that the model was able to distinguish between respondents who converted and those who did not convert. The model as a whole explained between 13.7% (Cox and Snell R square) and 24.2% (Nagelkerke R squared) of the variance in conversion status, and correctly classified 88.1% of cases. As shown in Table 5.2, total positive symptoms was the strongest predictor of conversion, with an odds ratio of 1.208. Of the baseline psychiatric disorders entered into the regression, only the absence of a baseline mood disorder was a significant predictor of conversion with an odds ratio of .225. Our hypothesis is partially supported as positive symptoms were found to be the strongest predictor of conversion, however the presence of a mood disorder predicted non-conversion to psychosis which was unexpected.

Chi-square analysis were then performed to assess the relationship between Axis I disorder and conversion status which are all categorical variables. These results were

statistically significant, revealing that only 35.3% of individuals with mood disorders at baseline converted to psychosis. This analysis further supported that there is a significant relationship between mood disorders and conversion status x^2 (1, n =156)= 4.688 p=.030.

Table 5.1

Correlations between Conversion and SOPS

	Conversion	Positive Symptoms	Negative Symptoms	Disorganized Symptoms	General Symptoms
Conversion	---				
Positive Symptoms	.263**	---			
Negative Symptoms	.171	.115	---		
Disorganized Symptoms	.202	.398**	.289**	---	
General Symptoms	-.035	.242*	.350**	.167	---

**Correlation is significant at the 0.01 level

*Correlation is significant at the 0.05 level

Table 5.2

Logistic Regression Predicting Likelihood of Conversion

	β	S.E.	Wald	df	*p*	Odds Ratio	95% CI for Odds Ratio	
							Lower	Upper
Sum Positive Symptoms	.189	.084	5.036	1	**.025**	1.208	1.024	1.425
Baseline Mood Disorder	-1.491	.650	5.267	1	**.022**	.225	.063	.804
Baseline Anxiety Disorder	-.067	.654	.010	1	.919	.936	.260	3.370
Baseline Substance Disorder	1.040	.950	1.198	1	.274	2.829	.440	18.212
Baseline Attention Deficit/Disruptive Behavior Disorder	-.786	.743	1.118	1	.290	.456	.106	1.956
Constant	-.2689	1.060	6.431	1	.011	.068		

p is significant at 0.05 level

Table 5.3

Baseline Axis I Disorders and Conversion

	Converter N=17 (10.9%)	Nonconverter N=139 (89.1)	χ^2	Fisher exact *p*-value
Mood disorder	6 (35.3%)	87 (62.6%)	4.688	**.038***
Anxiety disorder	9 (52.9%)	71 (51.1%)	.021	1.000
Substance use disorder	2 (11.8%)	9 (6.5%)	.647	.342
Attention-deficit and disruptive behavior disorder	6 (35.3%)	76 (54.7%)	2.282	.197

*p is significant at 0.05 level

Chapter 5: Discussion

This current study assessed the progression of Axis I and Axis II disorders in subjects who participated in the first phase of the Recognition and Prevention (RAP) Program from 2000-2006. This study used the RAP model to examine the rates of comorbidity, the development of psychiatric disorders, the relationship between psychiatric disorders and functioning, and the clinical predictors of conversion in a CHR sample consisting of participants who were in high- risk groups (CHR + and CHR-).

Prevalence Rates of Axis I and Axis II Disorders at Baseline

Our first hypothesis was partially confirmed and there essentially were no differences in rates of comorbid psychiatric disorders between the CHR+ and CHR- groups. However, there are some exceptions and noteworthy findings regarding the presentation of personality disorders. As mentioned previously, there is increasing evidence that personality disorder pathology is present in individuals who are high risk for developing psychosis (Klosterkötter et al., 2001; Lim et al., 2018; Ruhrmann et al., 2010; Ryan et al., 2015). In exploring the association between personality pathology and high-risk status, this current study found that there are significant differences between the high-risk groups in the presentation of borderline personality disorders, and paranoid personality disorders, and schizoid personality disorders. Results from this study convey that CHR- participants are more likely to meet criteria for schizoid personality disorder and CHR+ subjects are more likely to meet criteria for paranoid personality disorder and borderline personality disorder.

Regarding schizoid personality disorder, the symptoms are similar to the attenuated negative symptoms associated with the CHR- subgroup. In order to meet

criteria for the CHR-subgroup, participants must endorse at least one of the following negative symptoms with a score of 3 or above: social anhedonia, avolition, expression of emotion, experience of emotions and self, ideational richness, and occupational functioning (Miller et al., 1999). Similarly, individuals with schizoid personality features present with interpersonal, social, and affective deficits which are also consistent with the features of negative symptoms. Those who meet criteria for this disorder appear to isolate from others, display restricted range of emotional expression marked by flattened affect and appear detached (American Psychiatric Association, 2000; Esterberg et al., 2010). Earlier studies have confirmed the link between schizoid personality symptoms and negative symptoms (Cannon et al., 1990; Cuesta et al., 1999; Cuesta et al, 2002). Peralta et al. (1991) explained that "the negative schizophrenic symptoms are merely the persistence or exacerbation of schizoid traits present prior to the emergence of psychotic symptoms", (p.338). This overlap in symptomatology explains why participants in the CHR- subgroup were more likely to present with schizoid personality disorder and further supports that symptoms associated with schizoid traits are early manifestations of negative symptoms.

Subjects in the CHR+ group were more likely to meet criteria for paranoid personality disorder which is consistent with the positive symptom classification of this disorder. For CHR- participants to meet criteria for paranoid personality disorder would imply that subjects endorsed at least one attenuated positive symptom which by definition conflicts with the CHR- subgroup category (Lencz et al., 2004). Attenuated positive symptoms that overlap with paranoid personality disorder include suspiciousness and

mistrust of others, and unusual thought content (American Psychiatric Association, 2013; Esterberg et al., 2010; Miller et al., 1999).

Results also indicated that participants in the CHR+ subgroup were more likely to endorse borderline personality disorder compared to those in the CHR-subgroup. As stated previously, there is shared symptom presentation between borderline personality disorder and attenuated positive symptoms which may make it challenging to distinguish between personality pathology and psychosis pathology (Ryan et al., 2017; Thompson et al., 2012). A fairly recent study conducted by Paust and colleagues in 2019 also confirmed this position. This study examined borderline personality symptoms and transition to psychosis in a sample of at-risk youth. Borderline personality dimensions were assessed using the Borderline Symptom Checklist (BSL-95) and results supported that positive symptoms such as unusual thought content, suspiciousness/persecutory ideas, and hallucinations were strongly correlated with BSL scores (Paust et al., 2019)

Overall, the overlap in personality pathology symptoms with attenuated positive or negative symptoms suggests that additional longitudinal studies are necessary to clarify the relationship over the long term, especially for those who do not develop psychosis. The latter group of non-converters may represent false positives for psychosis who were inaccurately classified as high risk for psychosis. Furthermore, it may be beneficial to screen individuals who present with paranoid, schizoid, and borderline personality pathology for high-risk status given that some studies (although not this one) find an association between these disorders and psychosis. Lastly, these findings have important treatment implications as interventions will need to address all comorbidities and could inform specific treatment interventions.

Additionally, there is evidence of an observed difference in the presentation of oppositional defiant disorder (ODD) x^2 (1, n =155)= 3.835 p=.050, between the CHR subgroups, as CHR+ participants (30.7%) were more likely to meet criteria for ODD compared to CHR- participants (16.4%). The research specifically on ODD and high-risk is scarce but there are a few studies that do report prevalence rates of ODD between 2-5% (Addington et al., 2017; Preda et al., 2002; Staddard et al., 2010). A recent longitudinal study, assessing psychiatric diagnoses in children and adolescents from age 8 to 13 determined that ODD was associated with psychotic experiences in adults (Siebald et al., 2016). While there appears to be some association between ODD and high-risk for psychosis, additional studies may be able to elucidate the relationship between ODD and the CHR+ subgroup.

Although no significant associations were found between high-risk subgroup and Axis 1 diagnoses, the chi-square analyses display frequencies offering exploratory information regarding baseline diagnoses presentation within the high-risk groups. Consistent with previous studies, mood and anxiety disorders were the most prevalent at baseline (Addington et al., 2011; Fusar-Poli et al., 2014; Lencz et al., 2004; Lin et al., 2015). For the CHR+ subgroup 62.4% of participants met criteria for a mood disorder, and 54.5% endorsed a mood disorder in the CHR- subgroup. These results are also consistent with previous findings that MDD is typically the most prevalent mood disorder diagnosis among CHR participants (Kline et al., 2018; Lin et al., 2015; Meyer et al., 2005; Rosen et al., 2005). For anxiety disorders, 54.5% of subjects were in the CHR+ subgroup and 45.5% were in the CHR- subgroup. There were similar rates for combined mood and anxiety disorders (CHR+ = 79.2, CHR- = 78.2). This is also consistent with the

current research that individuals at-risk for psychosis present with combined anxiety and affective disorders. Additionally, social phobia was the most prevalent anxiety disorder (CHR+ = 22.8%, CHR- = 34.5%) which supports previous studies (Hui et al., 2013; McAusland et al., 2017; Meyer et al., 2004).

There is evidence to support that CHR subjects endorse attention-deficit and disruptive behavior disorders. For ADHD prevalence rates were (CHR+ = 33.7% and CHR- = 25.5%) and as stated previously for oppositional defiant disorder (CHR+ = 30.7% and CHR- =16.4%). While there were no significant differences in occurrence of attention-deficit and disruptive behavior disorders , these results support previous studies that they are present in the CHR population (Meyer et al., 2005; Thompson et al., 2015). Surprisingly, there were lower rates of substance use disorders observed in this sample (CHR + = 8.9% and CHR- =3.6% compared to previous studies.

Association Between Attenuated Positive and Negative Symptoms and Functioning in Axis I and Axis II disorders

Our study supported previous findings that Cluster A personality disorders (paranoid, schizoid, schizotypal) are associated with impaired social functioning (Fonseca-Pedrero et al., 2010; Henry et al., 2008; Oltmanns et al., 2002). These findings are expected as individuals who meet criteria for these disorders often present in a socially dysfunctional manner which deviates from the norm (Esterberg et al., 2010). Individuals with paranoid personality disorder may be considered odd or eccentric and may lack close relationships due to mistrust of others. Those who meet criteria for schizoid personality disorder may present with detachment from social relationships and restricted range in emotional expression. Lastly, individuals with schizotypal personality

disorder may lack a desire to form close interactions and may find it challenging trying to relate to others (American Psychological Association, 2000). Additional studies have found that individuals who meet criteria for Cluster A personality disorders also present with persistent decline in social functioning (Oltmanns et al., 2002; Seivewright et al., 2004). These findings suggest that it is important to take into account social functioning when assessing personality pathology presentation.

Cluster A personality disorders were found to be associated with attenuated negative symptoms for both the CHR- and CHR+ subgroups. Expectedly, for the CHR+ group, there was a significant correlation between attenuated positive symptoms. Cluster A personality disorders are grouped together by shared positive and negative traits. A possible explanation for the shared presentation in negative symptoms may be an overlap between the social anhedonia scale and social functioning. As explained by Pelletier-Baldelli et al 2021 "it may be that reduced capacity to experience pleasure leads to diminished seeking out of interpersonal situations" (p. 101).

Notably, significant moderate associations were also found between social functioning and negative symptoms for both subgroups. Negative symptoms have proven to be a determinant of social functioning based on previous studies. In a sample consisting of 167 CHR individuals, Fulford et al (2013) showed that severity of negative symptoms was significantly predictive of social functioning at baseline and follow-up. Furthermore, another study found negative symptoms to be a mediator between social function and global neurocognition (Meyer et al., 2014). Schlosser and colleagues also found negative symptoms to be a significant predictor of social functioning above and beyond mood symptoms. Additionally, experiential negative symptoms such as avolition, anhedonia

were more predictive of social functioning in comparison to expressive symptoms (emotional expressivity and alogia) perhaps suggesting that avolition and anhedonia are important determinants of social functioning. Additionally, experiential negative symptoms were also found to be a mediator between expressive symptoms and social functioning (Schlosser et al. 2015). These results imply that it could be beneficial to create targeted social interventions for high-risk participants.

Results also showed a strong association between Cluster C personality disorders and anxiety disorders which is supported by previous studies. As mentioned by Brandes & Bienvenu (2006), Cluster C is referred to as the 'anxious cluster' comprising of avoidant personality, dependent personality, and obsessive compulsive personality disorders. While anxiety disorders are co-occuring in individuals who meet criteria for personality disorders, the highest proportion appears to be among those with Cluster C personality disorders (Bienvenu, O. J., & Stein, M. B. (2003; Friborg et al., 2013; Sanderson et al. 1994).

Lastly, in this study mood disorders were associated with lower role functioning for CHR- which is supported by previous research (Fulford et al. 2013). Specifically, depression was significantly associated with impairment in role functioning. When depression diagnoses was included in a regression analyses and negative symptoms were controlled, depression was found to be a significant predictor of social functioning. Therefore, additional studies need to be conducted to further evaluate the relationship between depression, negative symptoms, and functioning.

Course of Axis I and Axis II Disorders

Our study replicated findings from Lin et al. (2015), supporting that mood and anxiety disorders are persistent and recurrent from baseline to follow-up in both CHR subgroups. For CHR+ participants 48.3% of mood disorders and 34.5% of anxiety disorders were persistent and recurrent. Among CHR-participants, 23.1% of mood disorders and 46.2% of anxiety disorders were persistent. Our findings also conveyed that personality disorders and attention-deficit and disruptive behavior disorders were also persistent among the subgroups. It was also surprising that substance use rates were rather low in this sample and was persistent in 15% of CHR- participants.

In assessing high risk individuals, it would be imperative to continue to screen for psychiatric disorders in this population. We only had 42 individuals for these follow-up analyses and were underpowered to perform additional analyses. Further studies may be able to expand on this research and explore the impact the persistence of these disorders may have on response to treatment and early intervention strategies. Also, additional analyses may be able to make more meaningful interpretations about the course of diagnoses in these subgroups.

Predictors of Conversion

Expectedly, positive symptoms were found to be a strong predictor of conversion which is also consistent with previous studies. Yung et al. (2003) explored the duration of attenuated positive symptoms in CHR individuals and results demonstrated that a longer duration of these symptoms increased transition to psychosis. In another study, more severe positive symptoms were found to be predictors of conversion (Carrion et al 2016).

Although mood disorders were persistent in the RAP subgroups, it appears that the presence of mood disorders predicts non-conversion to psychosis. Thus, having a mood disorder appeared to be protective against psychosis, which likely indicates that mood disorders account for the CHR presentation rather than being true risk factors for psychosis. Further analyses on how mood disorders evolve during the other stages may help to clarify the role of mood disorders in this population.

As mentioned previously, the RAP model has expanded to include CHR+ mod and also the SLPs. In a more recent study, Carrión et al (2017) evaluated the course of symptoms, differences in treatment outcomes, and conversion at different stages of the model. In this paper, the RAP model has been updated to highlight the range in symptom severity from moderate to severe for attenuated positive symptoms or the CHR+ stage. The updated model is as follows CHR- → CHR+Mod → CHR+Sev→ SLP. CHR+Mod has a total positive symptom score of <10 and for CHR+Sev a total positive symptom score of ≥ 10. (For the purposes of this study, we are using the previous 3-stage model). Results from this study indicate that risk for conversion is dependent on the entry point in the model, with CHR- stage showing the lowest risk of conversion of 5.9% and the highest symptom stability (70%). Whereas the SLP subgroup has the lowest symptom stability and the highest conversion rate of 49%. For the CHR+ moderate and severe subgroups, conversion rates were 28% and 11% respectively. The RAP staging model suggests that interventions should be more specific to target symptom severity. With that being said, individuals with more severe symptoms will be provided with more aggressive treatment options. In this study, subjects in the CHR- and CHR+Mod subgroups responded well to antidepressant medications, implying that antidepressants

may be particularly effective in earlier stages. The differences in symptom presentation, response to interventions, and conversion rates suggests that these subgroups are separate entities and should not be clustered together when exploring targeted interventions. See Figure 2. Additional studies could explore how disorders progress through these different stages and also help to clarify whether or not high-risk individuals may be at a higher risk of conversion compared to young adults who present with similar co-occurring disorders without the high-risk status (Albert et al., 2018).

Strengths and Limitations

A major strength of this study was the long follow-up period which was instrumental in assessing outcomes over a longer period of time. A limitation of this study is the variability in follow-up times which revealed a smaller sample size and smaller sample size included in follow-up analyses. We suggest additional analyses with longer-term follow-up periods to hopefully replicate some of these findings and also further explore the progression of psychiatric disorders in the RAP subgroups.

Conclusion

These findings provide implications for further research on the developmental course of symptoms for high-risk individuals. The comorbid rates and persistence over follow up of Axis I and Axis II disorders in the high-risk population suggests that there needs to be further screening of these individuals. Findings revealed that functioning and attenuated symptoms presentation vary in the subgroups. This research provides further information on factors that can be used to create targeted interventions for individuals who are in different stages of high-risk. Additionally, since affective, anxiety, behavioral

concerns may be the impetus for seeking treatment, additional screening measures may help to explore developmental pathways that may impact the course of psychosis.

FIGURES

Figure 1. Recognition and Prevention (RAP) neurodevelopmental model (Repinted from Cornblatt et al., 2003)

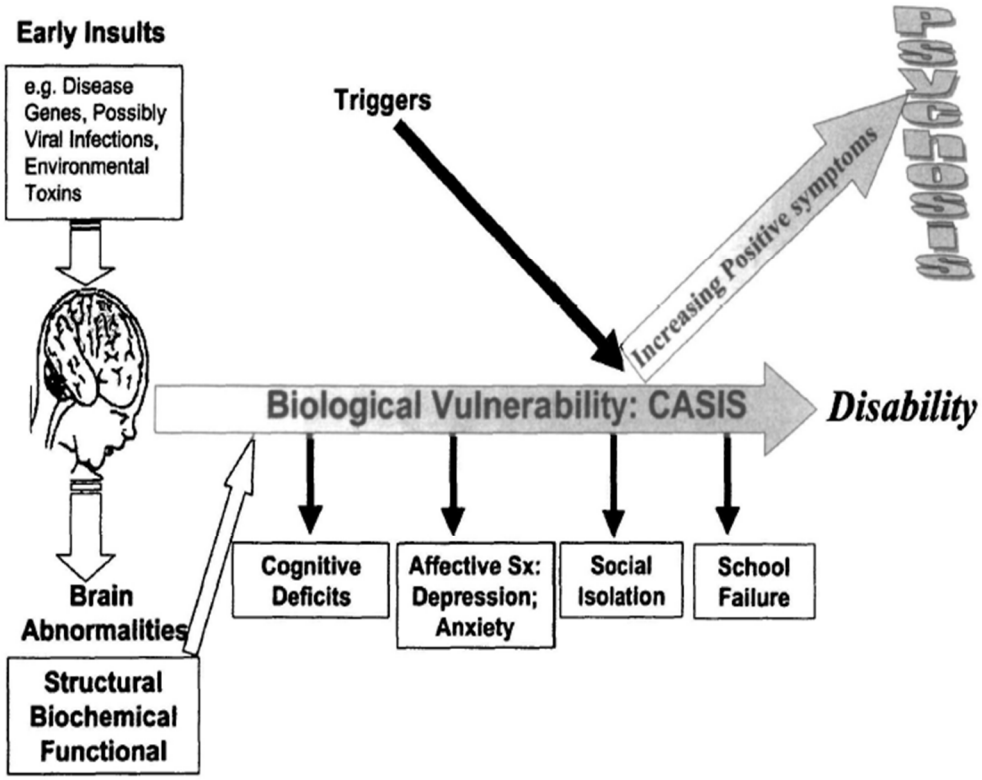
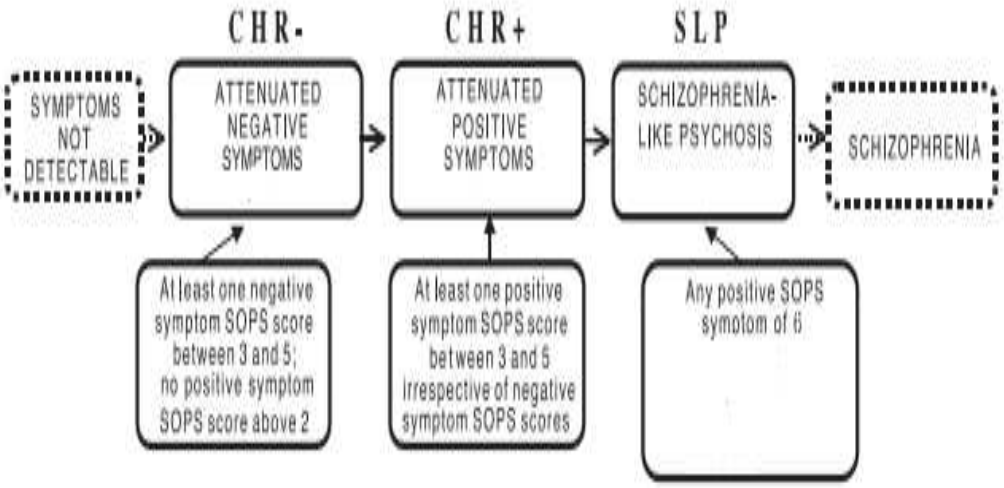


Figure 2. Recognition and Prevention (RAP) model of progression of high-risk symptoms (Modified from Lencz et al., 2004).



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