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The Role of Premorbid Adjustment in Predicting Post-Illness Psychosocial Functioning in the Early Stages of Psychosis

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To the Graduate Council:

I am submitting herewith a dissertation written by Stephanie Kristan Armstrong entitled "The Role of Premorbid Adjustment in Predicting Post-Illness Psychosocial Functioning in the Early Stages of Psychosis." I have examined the final electronic copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Social Work.

Sherry M. Cummings, Major Professor

We have read this dissertation and recommend its acceptance:

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(Original signatures are on file with official student records.)

**The Role of Premorbid Adjustment in Predicting Post-Illness Psychosocial
Functioning in the Early Stages of Psychosis**

**A Dissertation Presented for the
Doctor of Philosophy
Degree
The University of Tennessee, Knoxville**

**Stephanie Kristan Armstrong
May 2021**

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ABSTRACT

Schizophrenia is a chronic, debilitating illness with significant heterogeneity of onset, illness course, and outcome. Although affecting 1% of the population, disability costs ranked 11th of all health disorders internationally. Efforts to best understand how this disease process causes poor outcomes are imperative. Premorbid functioning, social and academic adjustment throughout development before illness onset, may inform long-term outcomes in psychosis. Chapter I details a systematic review of this relationship in early psychosis patients. Findings were supportive of a robust relationship between premorbid functioning and post-illness psychosocial functioning, particularly when social or academic premorbid domain approaches were used. No identified study used a domain by developmental period approach to predict psychosocial outcomes. To address this gap and improve on identified methodological concerns in previous literature, two studies were conducted using primary data in a sample of early psychosis patients. Using a comprehensive domain by trajectory approach, the first study examined associations between premorbid social and academic patterns and post-onset psychosocial functioning in early psychosis patients at study entry. The second study examined these same relationships for distal outcomes longitudinally at two-year follow-up. Study entry results, reported in Chapter II, illustrated significant relationships between trajectories of premorbid functioning and global and social functioning. Specifically, global psychosocial functioning was predicted by the change of social adjustment over development and initial academic performance. Study entry social functioning was associated with initial social performance and change of social performance over development. The two-year follow-up study, Chapter III, illustrated these relationships hold up over time. Two-year global functioning was predicted by academic premorbid patterns. Two-year social functioning was associated with social premorbid patterns and initial academic performance. Occupational functioning was associated with academic premorbid patterns. These findings demonstrate the importance of premorbid functioning to inform longitudinal post-illness psychosocial

functioning. Findings from these studies suggest that using premorbid data is a fruitful endeavor to inform psychosocial recovery interventions, which can be specifically tailored to individual patients' strengths. Future studies should continue to assess these patterns at further follow-up throughout the course of illness and design causal model investigations with these variables.

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INTRODUCTION

Purpose of the Study

Schizophrenia is an illness characterized by symptoms of reality distortion, disorganization, and negative symptoms leading to substantial long-lasting impairments in everyday functioning, including the ability to interact socially, sustain employment, and maintain activities of daily living. While schizophrenia is a low incidence condition, affecting 1 percent of the population, the disability caused by this mental health disorder ranks 11th highest across physical and mental illnesses (H. Y. Chong et al., 2016; Eaton et al., 2008; Vos et al., 2015). This severe disability leads to high economic, resource, and quality of life burdens for patients, families, and society. However, not all patients with schizophrenia have the same course or outcome. There is considerable heterogeneity following an initial episode of psychosis including continuous, multiple episode, or single episode presentations. Nearly 50% of patients experience sustained recovery periods, and a third have a single episode of psychosis without recurrence (Fusar-Poli et al., 2016; Vita & Barlati, 2018). Predicting the course of illness for schizophrenia patients has been historically unsuccessful. A greater understanding of prognostic features would improve our ability to specifically tailor interventions and increase our understanding of this potentially devastating illness.

The introduction of antipsychotic medication has proven moderately effective for treating the clinical symptoms of psychosis (delusions, hallucinations, etc.), but psychosocial outcomes (work, interpersonal relationships, etc.) have largely remained stagnant for the past 70 years as these are not responsive to pharmacological treatment (Fusar-Poli, McGorry, & Kane, 2017). Additionally, the relationship between clinical symptoms and psychosocial outcomes are weak (Alvarez-Jimenez et al., 2012; Carpenter & Strauss, 1991; M. Green, Kern, Braff, & Mintz, 2000; Michael Foster Green, 1996; Harvey & Strassnig, 2012). Therefore, more attention should be given to premorbid factors which may provide better predictive relationships to psychosocial outcomes. Premorbid adjustment is a robust

indicator of clinical prognosis tied to etiological hypotheses of schizophrenia and may be more useful for understanding heterogeneity within schizophrenia (MacBeth & Gumley, 2008; Malla & Payne, 2005; McGlashan, 2008; Van Mastrigt & Addington, 2002). Premorbid functioning represents an individual's level of psychosocial functioning before the onset of psychosis disrupts the typical pattern of development. This premorbid information could be harnessed to parse the heterogeneity within psychotic disorders more effectively. We know that individuals who present with a more acute, abrupt onset of psychosis have better opportunities for recovery than those with long-standing difficulties and an insidious, gradual decline into psychosis (Buoli, Serati, Caldiroli, Cremaschi, & Altamura, 2017; McGlashan, 2008). Focusing on these patterns through detailed investigations of premorbid functioning are imperative to understanding how premorbid factors may relate to specific difficulties or strengths in psychosocial functioning after the onset of psychosis.

While premorbid adjustment is a well-known prognostic factor, detailed investigations by specific domain and development stage in the premorbid phase are limited in previous work in this area. Even less is known about premorbid domains and trajectories as they relate to psychosocial functioning specifically. A systematic review was completed in 2007 that focused on the relationship of global psychosocial functioning in early psychosis and premorbid adjustment in 10 studies (MacBeth & Gumley, 2008). The authors report a modest effect of premorbid adjustment on global functioning in early psychosis but highlight the number of studies providing detailed data from these concepts is relatively small and most studies did not report the full available data from the premorbid adjustment assessment (MacBeth & Gumley, 2008). In this review, many flaws were identified from the included studies which will be improved upon in the current proposal (MacBeth & Gumley, 2008). Briefly, the psychosocial outcomes were characterized by two problematic measurement scales: the Global Assessment Scale (GAS) and Global Assessment of Functioning (GAF), which are two versions of the same scale (GAF is brief revision to GAS) (Endicott, Spitzer, Fleiss, & Cohen, 1976). These scales include a

single global number to represent psychosocial functioning, losing the important differences in functioning across sub-domains of functioning (i.e., social, occupational). A key measurement flaw in these two scales is the inclusion of clinical symptoms within the ratings, so that the scale does not purely measure psychosocial functioning. We know clinical symptoms and functional ability are not always at the same severity level, so this is a major flaw for measurement of psychosocial functioning. Finally, the large majority of the 10 studies included in the review, used an average of all premorbid adjustment items or report only on one domain, rather than investigating more specific patterns by social and academic domains or assessing developmental functional changes across the premorbid period (MacBeth & Gumley, 2008). It's logical to imagine different functioning levels across these areas which may be linked to different ultimate post-onset outcomes (MacBeth & Gumley, 2008). The current proposal hopes to improve upon these methodological concerns in investigating these relationships.

Theoretical and Conceptual Framework

Schizophrenia is a unique, complicated illness that has no known cause or cure. In fact, anti-psychotic medication, the first line treatment for psychosis, was discovered accidentally, and scientists still remain unclear of the mechanisms which alleviate psychotic symptoms (W. T. Carpenter & Davis, 2012). Despite that, over a hundred years of research about schizophrenia has produced some unifying theories from which to base this work.

The current understanding of the etiology of schizophrenia is best explained by the stress diathesis model. This model proposes that individuals who will develop schizophrenia have an underlying genetic susceptibility which is later activated by stressors during development, particularly in late adolescence or young adulthood (Nuechterlein & Dawson, 1984; Zubin & Spring, 1977). Research has shown heritability rates of 50% for monozygotic twins, the highest rate of prediction (Chou et al., 2017). The genetic prediction rate is 25% if your parent has schizophrenia and decreases dramatically as the shared genetics decrease (Chou et al., 2017). Therefore, there is a genetic component, but so far,

scientists have not been able to identify which gene, or more likely set of genes, is responsible for schizophrenia. Environmental stressors also play a large part in the development of schizophrenia(Nuechterlein & Dawson, 1984). The commonly accepted understanding of schizophrenia etiology is some level of genetic susceptibility which is then trigger by an environmental stressor to cause the onset of the disorder(Nuechterlein & Dawson, 1984; Zubin & Spring, 1977).

Within schizophrenia, there are two competing, yet complimentary models of course of illness: a neurodevelopmental or a neurodegenerative process. These two models attempt to classify the patterns of illness course. The neurodevelopmental hypothesis proposes a course of schizophrenia more aligned with a purely genetic etiology wherein patients with schizophrenia are cognitively and socially different from birth. Even before the onset of schizophrenia, the neural differences are present and apparent before the symptoms of psychosis present(Rapoport, Addington, Frangou, & Psych, 2005). This neurodevelopmental understanding of schizophrenia is commonly accepted in the general public. However, many patients have typical or even superior development until an abrupt change occurs (often a major stressor) resulting in psychosis where symptoms develop in days or weeks rather than months or years as in the neurodevelopmental process(Buoli et al., 2017). This latter model suggests that the cognitive and functional decline is a consequence of psychotic symptoms through a neurodegenerative process rather than genetics causing neural abnormalities from birth. It is most likely that both of these paths to schizophrenia exist, and both align with different outcomes(McGlashan, 2008). Understanding more about these two illness courses through premorbid factors can improve our understanding of the heterogeneity within schizophrenia.

Finally, the major theoretical basis for investigating the early stages of psychosis is the Critical Period Hypothesis proposed by Birchwood and colleagues(Birchwood, Todd, & Jackson, 1998). This theory postulates that the early years of psychotic illness, the first two to five years, are when the most damage to the brain occurs before settling in to a more leveled off, chronic state(Birchwood et al.,

1998). In this transitional period, early initiation of treatment, as soon after symptoms present as possible, dramatically increases the chances for remission and recovery. This theory follows a neuroprotective idea that active, untreated psychosis, is harmful to the brain. If medications and psychosocial interventions can be initiated as early as initial symptoms begin or before, outcomes are likely to improve drastically. By protecting the brain from damage that may occur from periods of untreated psychosis, remission of symptoms is likely and recovery more possible (Birchwood et al., 1998). Without early intervention and treatment, irreversible neural damage that negatively impacts one's ability to function is likely to occur leading to long-term psychosocial disability. Early intervention efforts are designed to halt this damage. Investigations of premorbid patterns may provide useful information for delivering more individually tailored psychosocial treatments to improve long-term psychosocial outcomes.

Objectives

The current work will set out to understand relationships between premorbid social and academic adjustment trajectories and longitudinal post-onset social, occupational, and global psychosocial functioning. Premorbid adjustment represents the developmental functioning from childhood through adulthood until 1 year prior to the onset of psychosis. Two primary domains of developmental functioning are of key interest for premorbid adjustment: social and academic. Premorbid adjustment patterns will be the primary independent variables in the current proposal. Psychosis onset is defined as the point at which the individual evidences the threshold level of psychotic symptoms that meet the criteria for a psychotic disorder. The post-onset course begins after the onset of psychosis. The early post-onset course, i.e. the early stages of psychosis, are discussed as being the first five years after onset of psychosis, with the two to five year course identified as the critical period for significant decline due to the disease process. The two time frames for data collection in this proposal include study entry and two-year follow-up, as this is a longitudinal outcome study. Study entry

is the date of the initial enrollment into the study which is designated as within two years of the psychosis onset. The follow-up period is designated as two-years after study entry, for investigation of longer term outcomes while still in the early phase of illness. Psychosocial functioning after the onset of psychotic illness for social, occupational, and global functioning are the primary dependent variables of interest. Scores for these measures are collected at two separate times - study entry and two-year follow-up to investigate: 1) overall abilities, 2) social abilities and ; 3) occupational abilities throughout the early stages of illness. Figure 1 illustrates these concepts and timelines visually with simulated data.

This proposal will improve upon previous studies in two major ways by: 1) using more detailed information of premorbid adjustment domains and patterns of functioning, expanding on traditional use of an overall average of all items and 2) improving and expanding the assessments used to define post-onset psychosocial functioning. This investigation will be a preliminary exploration of the impact of the social and academic premorbid patterns on post-onset psychosocial functioning measures globally, and specifically for sub-domains of social and occupational functioning. This preliminary exploration will examine these relationships at two crucial time points in the early stages of psychosis, at study entry (within two years of psychosis onset) and two-years later, for longitudinal, more distal outcomes. Premorbid adjustment will be separated in two domains - academic and social. For each domain an intercept and slope will be created to represent the starting point in childhood and the pattern of functioning over time, i.e. from the starting point of childhood to the last point of the premorbid period. These variables are created to represent the pattern of premorbid adjustment for social and academic functioning over the premorbid period including childhood, adolescence, and adulthood.

The dependent measures of interest are post-onset (study entry and two-year follow-up) social, occupational, and global psychosocial functioning measured by psychometrically improved and more specific assessment tools. This proposal will investigate post-onset psychosocial functioning longitudinally at study entry and two-year follow-up to assess for changes throughout the illness course

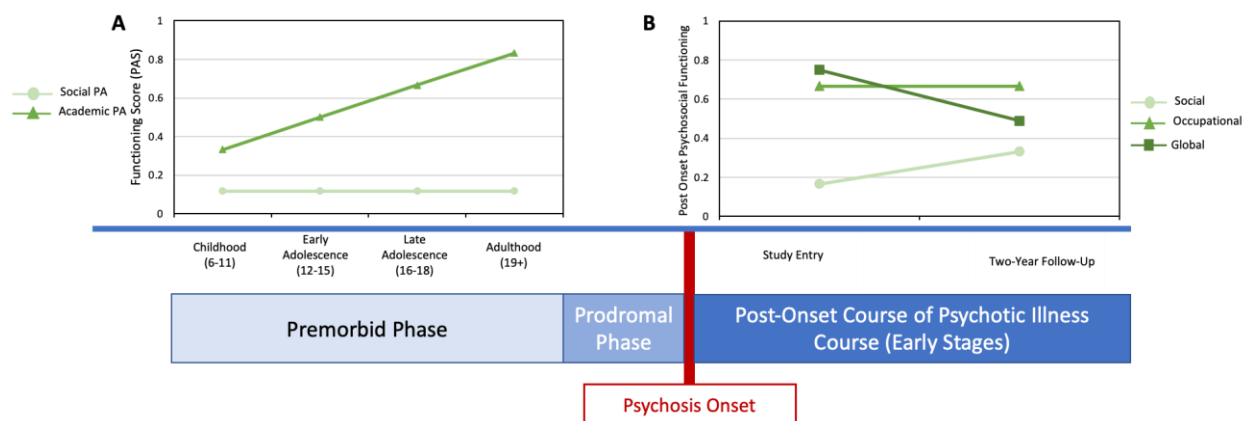


Figure 1. Conceptual Figure with Simulated Data. Blue and red boxes outline four periods throughout the life course of an early-stage psychosis patient: Premorbid Phase: development period before psychosis onset. The premorbid phase illustrates simulated data from the *Premorbid Adjustment Scale* for social (Panel A circles) and academic (Panel A triangles) premorbid adjustment (PA) over the four specified developmental time frames, up to 1 year before psychosis onset. Prodromal Phase: subtle, sub-threshold symptoms emerge. The prodromal phase is the one-year gap between premorbid functioning and psychosis onset. Psychosis Onset: threshold level psychosis. Psychosis Onset is determined by the *Structured Clinical Interview for DSM-IV-TR* as the date an individual reaches threshold level psychotic symptoms. Post Onset Course of Illness The early stages of psychosis include at least two years and up to 4 years in the current study over the follow-up period, depending on psychosis duration at study entry. Social (Panel B circles), Occupational (Panel B triangles), and Global Functioning (Panel B squares) are measured at Study Entry and Two-Year Follow-Up. In both panels, the Y-axis represents functioning levels with 0 as good performance and 1 as poor performance.

in the early stages of psychosis. With these important methodological improvements, the present proposal will set out to address if these premorbid patterns are associated with post-onset psychosocial functioning in the early stages of psychosis. The proposed work will also investigate if similar patterns of premorbid adjustment are associated differentially across areas of post-onset psychosocial functioning (social, occupational, or global) at study entry and two-year follow-up.

The following specific research questions are the primary objectives of the proposed investigation which will be investigated via two separate studies:

Study 1: Study Entry

- 1.) Are premorbid social and/or academic adjustment patterns associated with post-onset social, occupational, and/or global psychosocial functioning at study entry ?
 - a. Are social and/or academic childhood level of premorbid adjustment (the initial level or intercept) associated with social, occupational, and global psychosocial functioning at study entry?
 - b. Are social and/or academic premorbid developmental patterns (trajectories or slope) associated with social, occupational, and global psychosocial functioning at study entry?
 - c. Are social and/or academic patterns of premorbid adjustment differentially related to social, occupational, and global psychosocial functioning at study entry?

Study 2: Two-Year Follow-Up

- 2.) Are social and/or academic premorbid adjustment patterns associated with post-onset social, occupational, and/or global psychosocial functioning at two-year follow-up?
 - a. Are social and/or academic childhood level of premorbid adjustment (the initial level or intercept) associated with social, occupational, and global psychosocial functioning at two-year follow-up?

- b. Are social and/or academic premorbid developmental patterns (trajectories or slope) associated with social, occupational, and global psychosocial functioning at two-year follow-up?
- c. Are social and/or academic patterns of premorbid adjustment differentially related to social, occupational, and/or global psychosocial functioning at two-year follow-up?

The proposed research will investigate if premorbid social and academic patterns are associated with longitudinal psychosocial outcomes in the early stages of psychosis. The prospective, longitudinal design of this study provides an opportunity to investigate how premorbid adjustment is associated with post-onset psychosocial functioning at study entry (Study 1) and after two years of follow-up (Study 2). Study 1 will include three models (one for each psychosocial outcome as the dependent variable) to investigate psychosocial outcomes at study entry and Study 2 will follow the same pattern with three similar models. Four independent variables of premorbid adjustment (academic and social slopes and intercepts) will be included in all 6 models. The goal of this research is to explore the relationship of premorbid social and academic patterns to psychosocial functioning throughout the early course of psychosis to provide better understanding of potential strengths and opportunities for specifically tailored interventions in the long-term.

CHAPTER I

THE ROLE OF PREMORBID ADJUSTMENT IN PREDICTING POST-ILLNESS

PSYCHOSOCIAL FUNCTIONING IN THE EARLY STAGES OF PSYCHOSIS: A

SYSTEMATIC REVIEW

Abstract

Schizophrenia is a highly heterogeneous, yet often debilitating disorder with major psychosocial difficulties often resulting in long-term disability. Efforts to understand what leads to this psychosocial dysfunction in order to best support recovery in psychosis patients is imperative. Premorbid functioning, or the ability to function socially and academically throughout development, may be one area to better inform areas of psychosocial difficulties in psychotic disorders. A previous systematic review completed in 2007 found premorbid functioning shows consistent, moderate associations to global psychosocial functioning, although many methodological concerns were noted in the previous review. The current study provides an updated systematic review targeted at improving these methodological issues while focusing on sub-domains of premorbid functioning in early psychosis patients. Inclusion criteria for this systematic review included: publication date after 2007, use of the Premorbid Adjustment Scale (PAS) to measure premorbid functioning and premorbid functioning operationalized beyond an overall average, samples included a majority of non-affective psychosis, a diagnostic system to verify psychosis diagnoses was used and duration of illness no longer than 5 years, and use of an objective psychosocial functioning measure other than the standard Global Assessment of Functioning (GAF) or Global Assessment Scale (GAS). A total of 610 articles were identified from the search process, resulting in 14 studies after thorough screening for inclusion criteria. Results overwhelmingly demonstrated significant relationships between premorbid functioning and post-onset psychosocial functioning in 12/14 studies. Two main approaches to the premorbid data were used including by domain (social versus academic premorbid functioning) or by developmental stage. Ten studies used a domain approach with both academic and social premorbid functioning demonstrating significant relationships to post-onset functioning, but social premorbid functioning was reported most frequently. Just four studies used a developmental approach, investigating functioning at each development stage, and the late adolescence time period was most consistently reported to be related to psychosocial functioning. The findings from this review

highlight the consistent and strong association between premorbid functioning and post-onset psychosocial functioning in early psychosis. Social premorbid functioning was a consistent finding across many including studies and late adolescence was noted as a specific development stage with consistent relationships to psychosocial functioning. Importantly, no single study was identified which used both a domain by development stage approach to exploring these relationships, leaving out important information from the PAS. Future studies should use the full available information from the PAS to explore the informative nature of domain by trajectory of pre-illness functioning in early psychosis.

Introduction

Schizophrenia Impact

Schizophrenia is a highly disabling condition that affects roughly 1% of the population yet is the 11th leading cause of disability, with a significant worldwide economic burden of \$102 billion annually in the US (H. Y. Chong et al., 2016; Eaton et al., 2008; Vos et al., 2015). Patients with schizophrenia have premature mortality rates with lifespans shortened by 28.5 years and 5% lifetime suicide risk (Hor & Taylor, 2010; Olfson, Gerhard, Huang, Crystal, & Stroup, 2015). In fact, unmedicated first episode schizophrenia patients have shown a 37-fold increase in death by suicide (Tiihonen et al., 2006). Schizophrenia is a disorder characterized by symptoms of reality distortion, disorganization, and negative symptoms, which must be present at least six months, and with significant psychosocial impairment due to the illness. Despite partial success of antipsychotic medication in reducing clinical symptoms, psychosocial outcomes in schizophrenia have remained stagnant for 70 years (Fusar-Poli, McGorry, & Kane, 2017). These psychosocial outcomes often cut short an individual's ability to sustain employment or educational programs, maintain meaningful interpersonal relationships, and make it difficult to take care of oneself or manage a household independently. In many cases, due to these significant difficulties, patients with schizophrenia may pursue, often, life-long disability benefits and require supervised or publicly funded housing or experience long-term, unstable housing or homelessness (Ayano, Tesfaw, & Shumet, 2019; Eaton et al., 2008). Despite this grave outlook, there is considerable heterogeneity of psychosocial outcomes for patients with schizophrenia. Many patients go on to recover with proper treatment. In fact, a recent review of recovery in schizophrenia notes a range of 13 to 50% recovery rates while nearly a third of individuals with an initial episode of psychosis will not have a subsequent episode (Fusar-Poli et al., 2016; Vita & Barlati, 2018). Therefore, it is important to understand what may predict the considerable heterogeneity in recovery and psychosocial outcome in schizophrenia.

Psychosocial Outcome in Schizophrenia

Psychosocial outcomes include areas of everyday functioning such as social, occupational, and independent living skills, which when difficulties arise, result in significant and sometimes lasting disability. Psychosocial outcome is conceptualized as an individual's ability to complete everyday tasks and complete productive activities necessary for maintaining the ability to survive independently. The major domains of everyday functioning are social, occupational, and independent living skills, and these three areas are the major constructs considered (with the addition of cognitive ability) for US disability applications (Harvey & Strassnig, 2012; SSA, n.d.). Social functioning is one's ability to successfully interact with others including family relationships, form and maintain friendships, romantic relationships, and acquaintances or everyday people (i.e. grocery store clerk, coworkers, one's doctor). Occupational functioning is one's ability to sustain paid part or full time employment, pursue educational activities, or maintain a home/family. Independent living skills refer to mundane tasks adults must complete to function in society. These have a large range from survival level tasks such as feeding or bathing and increase in complexity such as budgeting, obtaining independent housing, and grocery shopping. There are many reasons why someone with schizophrenia may not be able to complete psychosocial tasks independently including clinical symptoms of disorganization, paranoia, or negative symptoms which may lead to repeated, disruptive psychiatric hospitalizations; cognitive difficulties such as concentration, memory, or attention; side effects of medication which may cause drowsiness or emotional and cognitive dulling (Harvey & Strassnig, 2012).

Several studies and reviews have illustrated that functional outcomes cannot simply be explained by the active psychosis symptoms, and in fact, the relationship between these two variables is weak (Alvarez-Jimenez et al., 2012; William T. Carpenter & Strauss, 1991; Michael Foster Green, 1996; Michael Foster Green, Kern, Braff, & Mintz, 2000; Harvey & Strassnig, 2012). In fact, pre-illness variables are often more strongly related to functional outcomes than symptoms (William T. Carpenter & Strauss,

1991). Cognition is related to psychosocial functioning, but a meta-analysis of this relationship reports effect sizes vary between 0.2-0.4, illustrating a wide margin of predictability with much variance left to be explained (Michael Foster Green et al., 2000). This relationship is also established longitudinally in a review of the literature, although authors note, "...it is clear that community functioning also is affected by a host of factors apart from cognition," (Michael F. Green, Kern, & Heaton, 2004). Additionally, just as course for cognition and symptoms have shown, trajectories of psychosocial functioning present significant heterogeneity with a spectrum of outcomes that may vary over time (Harding, 1988; Harrow, Sands, Silverstein, & Goldberg, 1997).

Theory of Etiology

Schizophrenia is an illness that most commonly presents in late adolescence and young adulthood, a critical period of development (Hafner et al., 1994). The stress diathesis model is the current best working theory widely accepted in the research community for explaining the etiology of schizophrenia (Meehl, 1962). This model proposes that individuals who will develop schizophrenia have an underlying genetic susceptibility which is later activated by stressors during development (Nuechterlein & Dawson, 1984; Zubin & Spring, 1977). Despite a unifying theory of etiology, the onset and course of schizophrenia is highly variable. The neurodevelopmental hypothesis of schizophrenia proposes a genetic abnormality that affects individuals from the earliest phase of development impacting cognition and outcome throughout life (Rapoport et al., 2005). An alternative model of neurodegeneration suggests that the brain and cognition decline overtime due to the illness rather than simply being born at a genetic disadvantage (Buoli et al., 2017). These two hypotheses are important to consider when investigating the course of psychosis and what factors may impact the trajectory. Predicting who will develop schizophrenia from the general population remains difficult, if not impossible, with highest rates of 10% identification if using family based genetic risk approaches. Prediction even remains elusive with focused efforts in ultra-high risk populations, help seeking

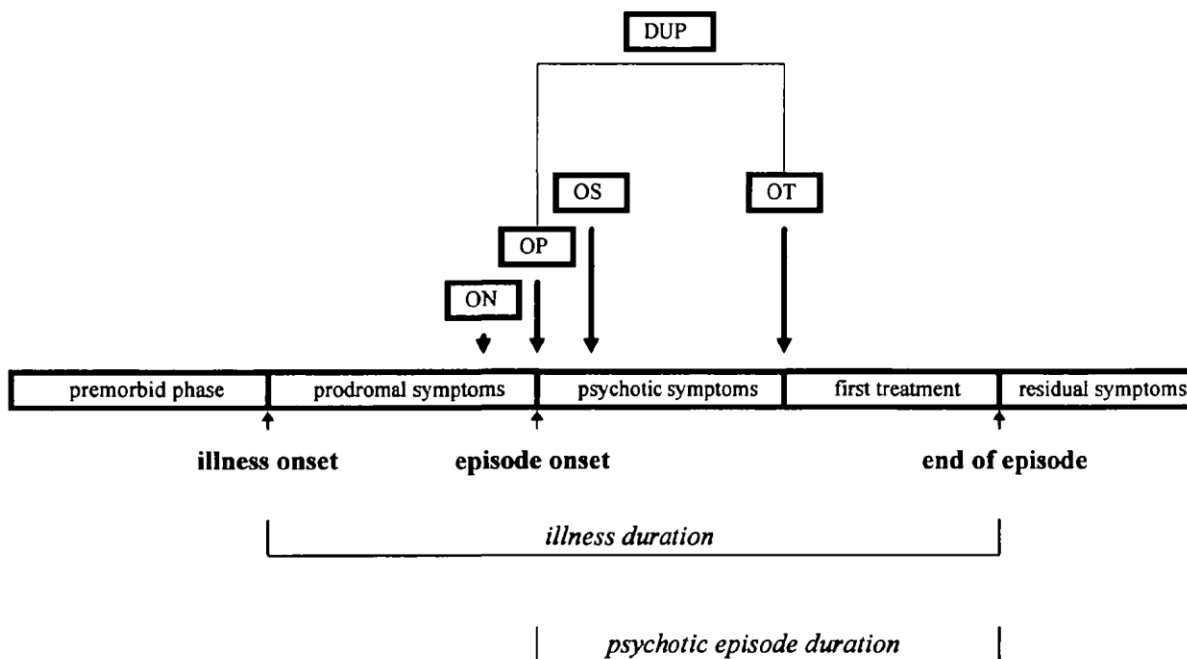
individuals with subtle symptoms, with only 20-35% ultimately converting to schizophrenia (Fusar-Poli et al., 2012, 2017). Therefore, we know that neither genetics or stress alone explain the development of schizophrenia, and it is likely a combination of the two that lead to the development of this illness.

Theory of Illness Development

The critical period hypothesis is posed as support for early intervention efforts in schizophrenia with the goal of halting, or at least reducing, the potentially severe, negative outcomes of long term disability caused by schizophrenia (Birchwood et al., 1998). This theory postulates that the early years of psychotic illness, the first five years, are when the most damage to the brain occurs before settling in to a more leveled off, permanent state (Birchwood et al., 1998). In this transitional period, typically during young adulthood, the earlier treatment is initiated and sustained, the chances for remission and recovery dramatically improve. This theory follows a neuroprotective idea that active, untreated psychosis is harmful to the brain. If medications and psychosocial interventions can be initiated as early as initial symptoms begin, outcomes are likely to improve, and improve drastically. By protecting the brain from damage that may occur from periods of untreated psychosis, remission of symptoms is likely and recovery more possible (Birchwood et al., 1998). Without early intervention and treatment, irreversible neural damage that negatively impacts one's ability to function is likely to occur leading to functional disability resulting in the need for longer term economic assistance.

Premorbid Adjustment

Premorbid adjustment is historically one of the most robust prognostic indicators of outcome in schizophrenia (MacBeth & Gumley, 2008; Malla & Payne, 2005; McGlashan, 2008; Van Mastrigt & Addington, 2002). Premorbid adjustment represents an individual's level of psychosocial functioning throughout development until illness onset. Figure 2 provides a visual for this developmental time period in the context of the course of psychosis.



- ON = onset of negative symptoms
- OP = onset of psychosis, positive symptoms
- OS = onset of psychotic syndrome
- OT = onset of treatment
- DUP = duration of untreated psychosis

Figure 2. Psychosis Course. Different stages of illness course in the early stages of psychosis are shown in the above figure. Important concepts to note are the premorbid period that occurs before prodromal or active psychosis. The post-illness phase begins at episode onset.

The primary areas of interest in premorbid adjustment are type of functioning, social or academic, and trajectory of functioning across development periods. Level of functioning in each domain is shown to predict various clinical outcomes (Allen, Kelley, Miyatake, Gurklis, & Van Kammen, 2001). The trajectory of functioning throughout childhood and adolescence is variable, and also provides important prognostic information about an individual. A stable course, either good or poor, is likely to present with different challenges than an individual who's functioning slowly deteriorates over childhood and early adolescence (Kelley, Gilbertson, Mouton, & Van Kammen, 1992; Rabinowitz et al., 2000). Therefore, how well a child/teenager is able to master social skills and interactions along with academic success throughout school, represents important developmental information about the individual.

These patterns of premorbid adjustment are tied to specific prognostic outcomes for schizophrenia patients (McGlashan, 2008). Some patients, representative of the neurodevelopmental hypothesis of schizophrenia, most linked to a genetic predisposition, struggle from the beginning of development until the onset of psychosis likely across social and cognitive domains and experience more severe psychosocial outcomes requiring numerous interventions and support (Rapoport et al., 2005). On the other hand, patients who function well pre-illness with a more abrupt onset, are likely to utilize their previous strengths and have better functional outcomes, in one or more domains, representing a neurodegenerative etiology with further progression with repetitive episodes (Buoli et al., 2017; McGlashan, 2008). Little focus has been placed on those who may do well in one versus another domain prior to the illness, however. Significant heterogeneity exists in premorbid functioning patterns. Deeper, more thorough understanding of premorbid patterns may provide insight into heterogeneity within schizophrenia that point to different etiologies, such as neurodevelopmental versus neurodegenerative hypotheses. While overall patterns of premorbid adjustment have garnered historical interest in predicting outcomes in schizophrenia, the details of developmental trajectories by

domain have received less attention in schizophrenia (Addington, Van Mastrigt, & Addington, 2003; Haas & Sweeney, 1992; T. K. Larsen et al., 2004).

Further understanding of premorbid functioning also presents an opportunity to consider pre-illness strengths or challenges that may provide insight into areas to focus intervention efforts.

Premorbid adjustment can be thought of as an overall concept, but perhaps would be most informative if broken down into its subunits. Individuals are likely to have various strengths and challenges rather than similar functioning across developmental periods and domains, all of which are informative.

Premorbid Adjustment and Psychosocial Outcome

A previous systematic review completed in 2008 by MacBeth and Gumley examined the relationship between premorbid adjustment and psychosocial outcomes in early psychosis (MacBeth & Gumley, 2008). This review identified ten studies that examined the relationship between premorbid functioning and global psychosocial outcome in early stage psychosis. Measures of global functioning included were the Global Assessment of Functioning (GAF) and Global Assessment Scale (GAS) (American Psychiatric Association, 2000; Endicott et al., 1976). Five studies examined relationships at baseline or study entry and found a negligible effect when using premorbid adjustment as an overall average score, but a small effect size was identified when separating premorbid functioning into typologies of good or poor functioning. Three studies examined this relationship longitudinally at one year follow-up and found a medium effect size between overall premorbid adjustment and global psychosocial functioning. Interestingly, pre-illness functioning during late adolescence specifically displayed a strong association with one year psychosocial outcomes. The authors concluded from these findings that there is a moderate effect between pre-illness functioning and post-diagnosis global psychosocial functioning in early stage psychosis. This effect is particularly strong for premorbid adjustment during late adolescence, and the strength of this effect increases with longer periods of follow-up (MacBeth & Gumley, 2008).

Measurement of Psychosocial Outcome

Assessment of psychosocial outcomes is completed in four primary ways: self-reports from patients, informant reports, objective ratings by clinician interviewer, and behavioral observation in natural environment or proxy measures of functional capacity (Bellack et al., 2007). Measurement for each of these has its own challenges but provide unique information. Pure objective measurement of everyday functioning is difficult to complete as direct observation in a natural environment can be very expensive and burdensome (Bellack et al., 2007). Functional capacity measures, what a patient may be able to do (ex. skills based demonstrations in a lab), are often used as a proxy for behavioral observation of functional outcomes, although there is a disconnect between capacity and actual behavior with low to medium correlations reported (Bellack et al., 2007; Bromley & Brekke, 2010). Subjective self-report measures in psychotic disorders have demonstrated problematic validity when compared to objective reports bringing this form of measurement into question (Bellack et al., 2007; Bromley & Brekke, 2010). Objective reports of psychosocial functioning, scored by a clinician are common for symptom assessments in psychosis and are an improvement over self-reports when considering clinician judgement and assessment guidelines. This is a feasible method with reasonable validity and reliability that attempts to measure functional performance rather than capability and without the pitfalls of pure self-reports (Bellack et al., 2007).

Methodology Concerns in Previous Literature

Despite the positive results from the MacBeth and Gumley (2008) review, methodological concerns exist. The measurement scales used to measure global functioning in the included studies, the GAS and GAF, are nearly the same scale with the GAF including modifications from the original version, the GAS (Endicott et al., 1976). Both scales are problematic when examining psychosocial functioning, as they both provide an overall score based on either or both psychiatric symptoms and psychosocial functioning, whichever is worse, when choosing a score. This psychometric concern is potentially

problematic when attempting to examine purely psychosocial functioning relationships as the scores from these scales may be influenced by active symptoms of psychopathology in addition to difficulties with psychosocial functioning. A newer version of the GAF was created which split the GAF into two scales – one for symptoms and one for social and role functioning – to address this issue. However, this separated scale was not used by studies included in the MacBeth and Gumley review likely due to the popularity of the GAF with its inclusion as Axis V in the DSM-III, DSM-IV, and DSM-IV-TR (American Psychiatric Association, 1987, 2000; Karterud, Pedersen, Loevdahl, & Friis, 1998).

The authors also examined quality of life as a separate outcome (MacBeth & Gumley, 2008). Global functioning and quality of life concepts frequently overlap in the literature; therefore, a review of these findings is warranted. Two quality of life scales were predominantly used by 10 studies that examined the relationship between quality of life and premorbid adjustment. The Quality of Life Scale is an objective, interviewer-rated scale that measures direct functioning and more abstract quality of life concepts such as satisfaction, etc., and was used by 7 studies (Heinrichs, Hanlon, & Carpenter, 1984). The Wisconsin Quality of Life scale has subjective and objective components for both actual functioning and satisfaction with functioning and other aspects of life, which was used by 2 studies (1 subjective and 1 interviewer-rated) (Diamond & Becker, 1999). A small to medium effect size was identified between quality of life and premorbid functioning (MacBeth & Gumley, 2008). The strength of this relationship increased over one-year follow-up. Similar to global functioning, the most robust premorbid adjustment relationship to quality of life was during late adolescence suggesting this developmental period's importance in predicting quality of life and global functioning (MacBeth & Gumley, 2008).

This review examined the important relationship between pre-illness or premorbid adjustment and post psychosis diagnosis global psychosocial functioning (MacBeth & Gumley, 2008). Many issues were raised by the authors following their review, however, that are important considerations for future studies. First, the included studies used a variety of measures for premorbid functioning despite a gold-

standard tool accepted in the research community, the Premorbid Adjustment Scale (PAS) (Cannon-Spoor, Potkin, & Wyatt, 1982). Other scales that have been used historically to measure premorbid adjustment also measure personality traits, etc., that are less directly relevant to actual social and academic functioning. Comprehensive use of premorbid measures of functioning are also lacking in previous studies. The measurement of premorbid adjustment includes social and academic domains as well as developmental changes over time. However, most of the included studies simply utilized an overall average score of premorbid adjustment, which ignores valuable information about different functioning domains and developmental aspects of stability or decline. These aspects of premorbid functioning are well known to affect prognosis in psychotic disorders and simplifying this information to an overall average is likely missing important, specific relationships. When studies did use the premorbid functioning data more elegantly, they still did not take all of the information into account in their analyses, simply focusing on averages from domains across all time periods or simply looking at average scores across development ignoring functional domain. A comprehensive examination which separates social and academic functioning across development was not utilized, which would provide a more complete look at different patterns of premorbid adjustment.

Concerns about psychosocial functioning measurement tools have been raised, but it is also important to point out that domains of functioning beyond a global score, such as occupational and social functioning, as separate outcomes were not reported in this review. This method may assume that functioning across domains is similar when separate types of functioning could vary greatly with differential impacts on patients' outcomes. This information would be important to investigate in future studies.

Purpose of Current Review

The purpose of the current review is to provide an update on the literature from the previous systematic review completed in 2008. While small to moderate effects were found for the relationship

between premorbid adjustment and global psychosocial functioning and quality of life in early psychosis, many methodological concerns were raised (MacBeth & Gumley, 2008). The number of included studies in this review is relatively small, especially when considering longitudinal outcomes. Because there are so few studies, examining sample composition demographics and inclusion criteria is important to consider. The authors point out that many studies simply consider premorbid adjustment as an overall score rather than a developmental trajectory with separate domains of functioning. Also, the range of outcome variables examined was quite narrow including rough estimates of global functioning. The current review looks to extend this knowledge base with more detailed uses of the premorbid adjustment scale with a specific interest in domain specific functioning, developmental trajectories of functioning, and in particular, studies that use both domain and developmental approaches together. An additional goal of this review is to investigate what domains of psychosocial functioning are associated with specific aspects of premorbid adjustment, extending findings beyond a global measure of functioning. Many more longitudinal studies following early psychosis patients from onset through distal outcome periods have now been completed. This review will also aim to highlight the premorbid adjustment relationship to longitudinal psychosocial outcomes across domains of functioning.

Method

The purpose of the current review is to provide an update to the literature since the MacBeth and Gumley review was completed (MacBeth & Gumley, 2008). The previous review's findings are limited as many studies simplified the Premorbid Adjustment Scale (PAS) to an overall score and measurement of psychosocial functioning was limited to global measures of the GAF and GAS scales, that include current psychosis symptoms in the measurement of psychosocial functioning (MacBeth & Gumley, 2008). The current review set out to identify all articles since 2007 that examined the relationship between premorbid adjustment and post-illness psychosocial functioning in non-affective early stages of psychosis, the precursor to schizophrenia and related psychoses. This systematic review

provides both an update from these findings and a more detailed understanding of this relationship through a comprehensive use of the PAS beyond an average score and including domains of psychosocial functioning.

Search Strategy

Databases included in the search were: Pubmed/Medline, PsychINFO, and CINAHL. Studies were included in the date range of 01/01/2007 until 08/31/2019. This time period was chosen as it provides an update to the previous systematic review on this topic that included studies through 2006. Search terms included: "early psychosis," "first episode psychosis," "premorbid adjustment," "premorbid functioning," "functioning," and "outcome."

Study Selection: Inclusion/Exclusion Criteria

Premorbid Adjustment: Pre-illness Functioning

Inclusion and exclusion criteria for study selection is detailed in Table 1.1. Premorbid adjustment may be measured in many ways. To ensure high consistency in the primary concept of interest, the use of the standardized interview and rating scale, the Premorbid Adjustment Scale (PAS) was required (Cannon-Spoor et al., 1982). The PAS is widely used in schizophrenia research and has good psychometric properties (interrater reliability: 0.74; validity evidence: discrimination of patients vs. healthy controls and known patient groups) and related to numerous clinical outcomes demonstrating prognostic validity of this scale (negative symptoms, course of illness, longer hospital stays, onset of psychosis, and brain abnormalities) (Cannon-Spoor et al., 1982; Shapiro et al., 2009). The PAS has been tested across genders with similar results, but no investigations have been conducted specifically by race or ethnic group (Krauss, Marwinski, Held, Rietschel, & Freyberger, 1998). PAS interviews were required to include the patient or the patient and caregiver for study inclusion. Studies that used only caregivers or medical/school record review to rate the PAS were excluded. Additionally, studies were required to use PAS data beyond a simple overall average, as this review is interested in developmental and/or

Table 1.1 Inclusion/Exclusion Criteria for Systematic Review

Criteria	Description
Inclusion Criteria	
Premorbid Adjustment	Measured with the Premorbid Adjustment Scale(Cannon-Spoor et al., 1982), including patient or patient and caregiver as informants
Psychosocial Functioning	PAS data reported beyond an overall average score Objective measures of functioning rated by interviewer
Early Psychosis	within three years of onset at study entry
Clinical Sample	Primary non-affective psychotic illness verified by standardized diagnostic system
Peer Reviewed	
English language	
Exclusion Criteria	
Premorbid Adjustment	PAS using only caregiver or medical record review alone
Psychosocial Functioning	Outcomes mixing clinical symptoms with functioning (including GAF, GAS) Self-report as only outcome
Early Psychosis	Enrollment criteria of greater than three years since onset Childhood or geriatric onset of psychosis
Clinical Sample	Failure to use standardized diagnostic system Majority affective illness

functional domains information of premorbid functioning. Traditionally, PAS data are treated as instructed by the developer, which includes norming scores from the 0 to 6 scale to a 0 to 1 scale for ease of interpretation, but no other normalizing procedures are described (Cannon-Spoor et al., 1982).

Psychosocial Functioning: Post-Illness Onset Functioning

A range of functional outcomes are of interest in this review including social, occupational/educational, and independent living/self-care. Due to the lack of consistency in functional outcome measures reported in the literature, all objective measures of functional outcome were included. Studies reporting only self-reports of functional outcome or subjective measures of quality of life were excluded. Studies which used the GAF or GAS scales, which mixed symptoms and functioning were excluded; however, studies using the split form of the GAF that reported GAF-symptoms and GAF-functioning scores separately were included (Karterud et al., 1998). Studies reporting objective quality of life measures were included if they tested functional outcomes separately from satisfaction related concepts. Studies reporting recovery or remission groups (defined by remission of clinical symptoms and return to psychosocial functioning for sustained periods) without separate reporting of psychosocial outcomes were excluded, to keep a clear focus on functional outcomes.

Clinical Population

Non-affective early stage psychosis is the clinical population of interest for this review. Individuals with chronic schizophrenia have severe outcomes; however, how and when in the illness course these occur is unclear. Identifying and following patients from their first presentation for prospective examinations of trajectories of illness and functioning are important to better understand this progression and deterioration of illness. Prospective studies with early psychosis patients also avoid study limitations common with chronically ill patients. Studying patients in the early stages reduces the amount of time that's passed when assessing premorbid adjustment and limits disease progression confounds of medication effects, functioning, and memory caused by years of illness. Defining early

psychosis is highly variable across research groups. Two crucial considerations are primary diagnosis and duration of symptoms at time of study enrollment. Non-affective psychosis (primary psychosis without full mood episode overlapping; precursor to schizophrenia spectrum disorders) is the primary focus of this review. However, studies which included a minority of affective psychosis (bipolar or major depression with psychosis) cases were considered for inclusion as well. It is common for diagnoses to evolve over the early course of illness, and it can be difficult to determine the diagnostic differences in the very early stages of psychosis (Fusar-Poli et al., 2016). Studies with predominantly affective samples were excluded, however, as it's well known that outcomes for these two groups are different (Bora, 2016). For inclusion, diagnosis of psychotic or mood disorder must have been made using a standardized diagnostic system (Diagnostic and Statistical Manual of Mental Disorders (DSM), International Classification of Diseases (ICD), etc.) to ensure quality of diagnosis and validity and consistency of clinical samples included in the review (American Psychiatric Association, 2000; World Health Organization, 2018). The early stages of psychosis are defined in various ways across research groups. This review defines the early stages by symptom duration of no more than three years at study enrollment, consistent with most studies of early psychosis and in line with the critical period hypothesis (Birchwood et al., 1998). Childhood and geriatric onset studies are excluded as these forms of psychosis are uniquely different from general psychotic disorders with peak incidence in late adolescence/early adulthood (Jablensky et al., 1992). Additional criteria for inclusion were English language and peer-reviewed articles.

Results

Study selection summary

A total of 605 articles were identified from the search strategy. These articles were analyzed for inclusion criteria by examining study abstracts. Review articles and repeats were excluded resulting in 342 articles. After a review of abstracts, studies that seemed to fit inclusion/exclusion criteria were

located and reviewed in full to ensure appropriate selection for the review. A remaining 14 studies from 8 research groups were determined to meet all specified search criteria for inclusion in the current review. The results below will be grouped by use of PAS data which included two primary techniques: functional domain (academic, social, and rarely socio-sexual) and developmental time period (childhood, early adolescence, late adolescence, and/or young adulthood). Organization within these areas includes studies from the same cohort presented together arranged by length of follow-up. Details of how the PAS was used, operationalization of each functional outcome reported (social, occupational, self-care/independent living, or global), and the relationships between the two will be summarized for each study. Relevant details of the clinical sample (proportion of non-affective psychosis, definition of “early psychosis,” diagnostic system utilized, etc.) are reported in Table 1.2.

Premorbid Functional Domains: Academic and Social

As suggested in the MacBeth and Gumley review, more detailed investigations of premorbid adjustment will be reviewed beginning with examinations broken into of domain functioning (MacBeth & Gumley, 2008). Social and academic functioning in childhood and adolescence likely have differential impacts on distinct areas of functioning in psychotic disorders although many studies from the previous review failed to report these domains separately, instead using only a global score (MacBeth & Gumley, 2008). In the current review, results from ten studies that investigated domains of premorbid adjustment are summarized below.

The GENIPE group (a multidisciplinary group of researchers in Spain) published two studies on the investigation of premorbid factors examining baseline psychosocial functioning in early psychosis. The first study examined the factor structure of the PAS and other clinical, cognitive, and functional variables correlated with each factor in a sample of both early psychosis (N = 33) and chronic schizophrenia patients (N = 51) (Barajas et al., 2013). For the purposes of this review, only the early psychosis findings will be discussed. This paper also looked at developmental trajectories through late

Table 1.2. Clinical Characteristics of Samples for Included Studies

Study; Cohort	Analysis Time Points	Sample size	Early Psychosis Definition	Diagnostic Method	DUP (wks)	Mean Age, %Male	Diagnostic Group (% Non-Aff)
Domain Approach							
Barajas, 2013; <i>GENIPE</i>	Baseline	33	<6 mons treatment, <1yr psychosis duration	DSM-IV-TR (no SCID)	Not reported (<1yr)	26.1; 61%	76%
Grau, 2016; <i>GENIPE</i>	Baseline	90	<6 mons treatment, <1yr psychosis duration	SCID for DSM-IV-TR	Not reported (<1yr)	20.6; 59%	70%
Simonsen, 2007; <i>TIPS</i>	Baseline, 3 mon, 1yr	298; 280; 266	<12 wks of adequate AP treatment	SCID for DSM-IV (entry)	47	27.8; 58%	86%
Ayasa-Arriola, 2013; <i>TIPS</i>	Baseline, 1yr, 3yr	284; 222; 202	<6 wks adequate AP treatment, in 1st episode	SCID for DSM-IV (6 mon)	34	29; 57%	100%
Jeppesen, 2008; <i>OPUS</i>	Baseline, 1yr, 2yr	423; 334; 294	<12 wks AP treatment	ICD-10, SCAN & WHO	48	26; 56%	100%
Albert, 2011; <i>OPUS</i>	Baseline; 5yr	468; 255	<12 wks AP treatment	ICD-10; SCAN	121	26; 56%	100%
Chang, 2016; <i>EASY</i>	Baseline, 6 mon, 1 yr	156	Psychotic symptoms without previous treatment, ages 15-25, duration unspecified	SCID for DSM IV	36	22.9; 52%	91%
Chang, 2018; <i>EASY</i>	Baseline, 3 yr	143	Psychotic symptoms without previous treatment, ages 15-25, duration unspecified	SCID for DSM IV	36	22.9, 52%	100%
Norman, 2012; <i>PEPP</i>	Baseline, 5 yr	132	<4 wks AP treatment	SCID for DSM IV (baseline, 1 yr)	67	23.8; 77%	94%
Norman, 2015; <i>PEPP</i>	Baseline, 5 yr	113, 79	"primarily untreated patients"	SCID for DSM IV (1 yr)	79	25.3; 78%	93%
Development Approach							
Canal-Rivero, 2018; <i>PAFIB</i>	Baseline, 1 yr	65	At least 1 psychotic symptom, 1st contact with provider	SCID for DSM-IV	0.57	26; 68%	86%
Pelayo-Teran, 2018; <i>PABIF</i>	Baseline, 3 yr	415; 307	<6 wks adequate AP treatment, "in 1 st episode"	SCID for DSM IV (6 mon)	54	30; 55%	100%
Chong, 2018; <i>EASY</i>	Baseline, 6 mon, 1 yr	269; 173; 112	Psychotic symptoms without previous treatment, ages 15-25, duration unspecified	DSM IV (no SCID)	25	34.2; 35%	Unclear (~ 77%)
Crumlish, 2009; <i>DETECT</i>	Baseline, 4 yr, 8 yr	118; 67	1st presentation to services & <1 mon of AP treatment	SCID for DSM IV	24.5	26.9; 61%	100%

DUP=Duration of Untreated Psychosis; AP = Antipsychotic; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision, SCID = Structured Clinical Interview for DSM, ICD = International Classification of Diseases, SCAN = Schedules for Clinical Assessment in Neuropsychiatry interview; Non-Aff = Non-Affective; Mon = months, Wks = weeks, Yr = years

adolescence, but these were not linked to functional outcomes so this part of the study will not be reviewed. Functional outcomes included in this study were limited to two measures of global functioning (Disability Assessment Schedule, DAS; Life Skills Profile, LSP) (Rosen, Hadzi-Pavlovic, & Parker, 1989; Üstün & World Health Organization, 2010). PAS Adulthood functioning was excluded from analysis. Subjects met DSM-IV criteria for psychosis, were within one year of their psychosis onset with less than six months of anti-psychotic treatment, and included 76% non-affective psychosis patients. This sample included 61% male with an average age of 26 and average DUP (Duration of Untreated Psychosis) or duration of psychosis was not reported. A three factor solution was chosen rather than the traditional social versus academic two-factor, which added socio-sexual functioning as a separate domain from social. Associations between premorbid factors and functioning were limited to the premorbid social factor with both overall DAS and LSP scores. The academic factor was correlated with many cognitive (premorbid IQ, memory, and executive functioning) variables while the socio-sexual factor was only correlated with positive symptoms. The social factor was also correlated with positive symptoms (Barajas et al., 2013). This study's strengths include the detailed investigation into the PAS; however, this is a very small sample size for a factor analytic study. The study stopped at correlations with factors rather than regression prediction models which would have been more informative. Additionally, only global functioning was reported despite sub-scale data availability. The cross-sectional design of this study is less informative of outcome than longitudinal, but initial outcome is also of interest.

The second study by the GENIPE group, used social and academic factors for premorbid adjustment, the five factor model of the PANSS (Positive and Negative Syndrome Scale), and a cognitive battery to predict psychosocial functioning using the DAS for both overall and subscales of self-care, occupational, and social functioning in a sample of 90 early psychosis patients (Grau et al., 2016; Kay, Fiszbein, & Opler, 1987). The requirements for early psychosis was the same as described above but 70%

of this sample met criteria for a non-affective psychotic disorder. This sample was younger with an average age of 20.6 and unreported DUP or duration of psychosis although less than 1 year of psychosis was a recruitment requirement. Specific use of the PAS was not discussed so it is unclear which developmental time periods were included. It is likely this study utilized the same method as the previous study from this group, however (Barajas et al., 2013). Correlations with disability measures informed predictor variables for inclusion in the multiple regression models. The model for overall functioning explained 43% of the variance and included positive symptoms, long-term memory, and social premorbid adjustment ($B = 4.57, p < 0.001$). Social premorbid adjustment was also a significant predictor for social functioning ($B = 2.1, p < 0.001$), but not for self-care or occupational functioning. The academic domain was correlated with occupational ($r = 0.24, p = 0.04$) and overall functioning ($r = 0.25, p = 0.03$) but did not reach the more stringent $p < 0.01$ level set to control for multiple comparisons and was therefore not included in the prediction models (Grau et al., 2016). No confidence intervals or effects were reported. Strengths of this study included the use of domains of premorbid adjustment and subscales of psychosocial outcomes. Study limitations include a relatively small and mixed diagnostic sample in a cross-sectional study design. It is possible that academic premorbid adjustment may have been included as a significant factor if the sample was limited to non-affective psychosis or with a larger sample size.

The TIPS program (Treatment and Intervention in Psychosis Study) in Oslo, Norway, recruited a large epidemiologic early psychosis sample ($N = 301$) to predict 1-year outcomes using measures of symptoms and functioning over the first year (baseline, 3 months, 1 year) (Simonsen et al., 2007). The study had high retention over the follow-up period ($N = 257$). Patients were required to have less than 3 months of antipsychotic treatment and be diagnosed with affective (14%) or non-affective psychosis (86%) meeting DSM-IV criteria confirmed by Structured Clinical Interview for DSM (SCID) at study entry; however, no diagnostic confirmation at 1 year follow-up was reported (First, M. B., Gibbon, R. L., Spitzer,

R. L., Williams, 1995). Mean age for this sample was slightly older than typical early psychosis samples at 27.8 and 58% of the sample were male with 47 weeks DUP at study entry. The PAS social and academic domains were used in two ways in this study: 1) Level of domain (average childhood score for each) and 2) Change of domain over time (difference in last included development period from childhood score). All developmental periods were included from the PAS. Functional outcome was measured using the split form of the GAF scale, and only the GAF-functioning (GAF-F) scores will be reviewed for functional outcome. Prediction of 1-year functional outcome revealed that all premorbid measures were significant at the step they were entered in the model. However, the final model included only childhood social functioning ($R^2 = 0.21, p < 0.01$) along with duration of untreated psychosis (DUP) and 3 month GAF-F scores (Simonsen et al., 2007). No confidence intervals or effects sizes were reported. The strengths of this study include the longitudinal design with multiple measurements over the follow-up period, the large, epidemiological sample with high retention, and detailed use of the PAS. Limitations include the GAF-F scale only gives an overall psychosocial functioning score and that the SCID was only completed at baseline when diagnoses are unstable. A 1-year diagnostic update would have improved our understanding of the cohort and examining differences in affective versus non-affective psychosis would have been important in this large sample.

The EASY group (Early Assessment Service for Young People with Early Psychosis) in Hong Kong completed a clinical trial of specialized services for early psychosis patients and reported on predictors of functional remission in their sample at 1-year and 3-year follow-up (Chang et al., 2016, 2018). Functional remission is related to functional outcome although the criteria for remission are quite stringent. This group defined functional remission as: working or studying full or part-time, Social and Occupational Functioning Assessment Scale (SOFAS) global score greater than 60, Role Functioning Scale (RFS) subscale scores of greater than 5 for self-care and immediate social network and greater than 4 for occupational and extended social network functioning at both 6-month and 1-year follow-up or for the

last six months for 3-year follow-up study (American Psychiatric Association, 2000; Goodman, Sewell, Cooley, & Leavitt, 1993). Social and academic domains of premorbid adjustment were used as a predictor in both models although it is unclear which development stages of PAS were used as this was not specified. The requirements for meeting early psychosis definition were vaguely stated as presence of psychotic symptoms without previous treatment, diagnoses confirmed by the SCID for DSM-IV. The samples had relatively short duration of untreated psychosis (36 weeks for both), but they do not specify the duration since onset of psychosis which is particularly problematic in this cohort recruited as part of a multi-year clinical intervention trial. The sample included a mean age of 22.9 and 52% male for both studies.

The 1-year follow-up study included 156 first episode psychosis patients (91% non-affective) with functional remission status met for 20% of the sample. Neither premorbid adjustment domain was a significant predictor of functional remission group but female gender, lower cluster C personality traits, extended time in the treatment trial, lower baseline positive symptoms, and better baseline functioning were (Chang et al., 2016). At three-year follow-up, 143 subjects (100% non-affective) were included with 22% meeting criteria for functional remission. The two significant predictors of functional remission group were lower levels of amotivation and better functioning at baseline. Premorbid domains were not significant (Chang et al., 2018).

Strengths of these studies include a large, well characterized majority non-affective first episode psychosis sample with longitudinal follow-up and detailed assessment of functional outcomes.

Limitations include the sample was enrolled after completion of a two-year clinical intervention study and randomly assigned to a one-year extension or standard treatment for an additional year.

Assignment of intervention group may differentially affect outcomes. Also, since the patients were enrolled after three years of treatment, this “first-episode” sample is much further along in the course of psychosis than most samples that attempt to recruit and study subjects as close to the onset as

possible. Also, the functional remission group is very small and the strict and difficult to meet criteria for functional remission may explain why no premorbid adjustment measure is found to be significant. The functional remission concept is different than investigating general functioning at any given timepoint considering the multiple criteria which have lengthy duration requirements. Results from these two studies should be considered with this in mind.

In a large sample of non-affective early psychosis patients within a Spanish antipsychotic medication trial (random assignment to one of five major antipsychotics), the First Episode Psychosis Clinical Program (PAFIP) cohort explored functional disability over a three-year follow-up period (Ayesa-Arriola et al., 2013). At baseline, 284 patients were included but only 158 were available for 3-year follow-up, 114 of which were characterized as having functional deficits. Patients with fewer than 6 weeks of antipsychotic treatment who were deemed to be in their first episode underwent diagnostic assessment with the SCID for DSM-IV six months after the baseline visit. The sample was older than most early psychosis samples with a mean age of 29 and 57% male with a reported DUP of 34 weeks. The DAS was used to group patients into disability groups based on 3-year DAS overall evaluation item of some disability (score of 1 or more) or no disability (score of 0). All developmental periods of the PAS were used in calculating an average score for social and academic domains. However, due to collinearity concerns of academic premorbid adjustment and years of education, only social premorbid adjustment was used in the analysis and educational attainment was used as a proxy for the academic domain. Patients with functional disability at 1-year ($N = 70$) and 3-year ($N = 86$) follow-up had significantly worse academic and social premorbid functioning scores. Premorbid social adjustment was a significant independent predictor of functional disability at 1 year ($B = 0.64$, $SE = 0.231$, $Wald = 7.63$, $p = 0.006$, $OR = 1.892$, $CI [1.203-2.974]$). Premorbid social adjustment and years of education were independent significant predictors of three-year functional disability (as well as diagnosis of schizophrenia) ($B = 0.448$, $SE = 0.197$, $Wald = 6.143$, $p = 0.013$, $OR = 1.628$, $95\% CI [1.107-2.395]$) (Ayesa-Arriola et al., 2013).

Strengths of this study include the repeated measurements over three-year follow-up. Limitations include the sample is within a pharmacological trial of random assignment to various antipsychotics which could have an effect on outcomes. The functional outcome measure was treated as a dichotomized variable from a continuous/ordinal measure of disability which oversimplifies the concept and likely masks some meaningful variability within the range of the item. Different areas of functioning were not investigated separately and the academic premorbid domain was not directly used as it was highly related to educational attainment. The SCID was not conducted at 3-year follow-up which limits certainty of diagnoses.

Two studies from the Danish Opus trial, a large randomized controlled trial of enriched versus standard treatment of early psychosis, looked at premorbid adjustment associations with functional outcome at 2-year and 5-year follow-up (Albert et al., 2011; Jeppesen et al., 2008). Early psychosis patients were included in the trial if they had less than 12 weeks of antipsychotic treatment and met ICD-10 criteria for a non-affective psychotic disorder as confirmed by the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview (World Health Organization, 1999).

The two-year follow-up study included 294 patients with a mean age of 26 and 56% male with average DUP of 48 weeks (Jeppesen et al., 2008). The adulthood and general subscales were excluded from the PAS, and social and academic domain scores were created. Functional outcomes included social functioning, measured by the Social Network Schedule (all social contacts with family and friends in past month), and occupational outcome, gathered from medical records or interview (Dunn, O'Driscoll, Dayson, Wills, & Leff, 1990). Both social and occupational outcome were categorized into good versus bad for binary logistic regression modeling. Results indicated that poor social premorbid adjustment predicted small social network at baseline and 1-year follow-up while poor academic premorbid functioning predicted poor occupational outcome at 1-year and 2-year follow-up (Jeppesen

et al., 2008). Results for these models were not presented, only narratively described (data presented only for models including positive and negative symptoms as dependent variables).

The five-year follow-up of the Opus trial included 255 non-affective psychosis patients with a mean age of 26 and 56% male with average DUP of 121 weeks. This follow-up study investigated recovery rates and predictors of recovery and work status separately (Albert et al., 2011). The concept of recovery includes remission of both clinical symptoms and functional deficits; therefore, only work status results will be reviewed here to remain consistent with reporting of strictly functional outcomes. Work status was reported by the patients but no standardized measure was used. Seventy-six of the 255 included patients were working at 5-year follow-up. All time periods of the PAS were included when creating functional domains. Both social ($Exp(B) = 0.81, p < 0.01, CI[0.7-.93]$) and academic ($Exp(B) = 0.85, p < 0.05, CI [0.74-0.97]$) premorbid adjustment domains were significant univariate predictors of work status. In the multivariate regression, higher age and negative symptoms were significant, independent predictors of work status but neither PAS domain was significant and no statistics were reported for this model (Albert et al., 2011).

Strengths of the included studies from the Opus trial are the longitudinal study design with a large, completely non-affective psychosis sample with long term follow-up periods. Sub-domains of both premorbid adjustment and functional outcome were investigated. However, the limitations include the differences in treatment through the clinical trial design may likely impact outcomes. No standardized measure of work status was used which limits the generalizability of this finding in both studies. The 5-year study also reported a large attrition rate over follow-up (5-year: 46%). It is unclear if the SCAN interview for diagnostic assessment was completed after study entry at any additional follow-up visit which would strengthen the clinical sample. The DUP is very different between the two studies which is puzzling (48 versus 121 weeks). The five-year follow-up includes an average of 2.7 years of untreated psychosis by study entry, which brings into question the duration of psychosis in this early sample.

The Prevention and Early Intervention Program for Psychoses (PEPP) cohort in Ontario, Canada, conducted two studies which utilized premorbid adjustment domains as predictors of multiple functional outcomes over 5-year follow-up (R. M.G. Norman et al., 2012; Ross M G Norman, Carr, & Manchanda, 2015). Early psychosis patients with less than 4 weeks of antipsychotic treatment were assessed at baseline and 1-year with the SCID for DSM-IV. The first study focused on the contributions of duration of untreated psychosis and untreated illness on 5-year symptoms and functioning in 132 primarily non-affective first episode psychosis patients (94%) with mean age of 23.8, 77% male, and mean DUP of 67 (R. M.G. Norman et al., 2012). Two functional outcome assessments were used, SOFAS and Life Chart Schedule (LCS). The SOFAS provides a global functioning score while the LCS provides duration of disability service use and full-time employment within the past year. PAS childhood and early adolescence time frames were included, and domain scores for social and academic average score were calculated. Multiple regression models to predict 5-year functional outcomes were tested to identify independent predictors of outcome. This study found that PAS academic and social functioning were associated with different functional domains at 5-year follow-up. The premorbid social measure was an independent predictor of 5-year overall psychosocial functioning ($B = -0.18, p < 0.05$) (R. M.G. Norman et al., 2012). No confidence intervals, effect sizes, or model statistics were presented in this paper. This finding suggests that different premorbid domains provide specific predictive power for distinct functional domains at follow-up. Strengths of this study include the longitudinal design, large sample size with long follow-up, and investigations of domains of premorbid and functional outcomes. However, no measures of social or self-care functional outcome or developmental trajectories were used for premorbid adjustment.

The second study by the PEPP cohort that utilized domains of premorbid adjustment, reported consistent use of functional assessments and use of the PAS (Ross M G Norman et al., 2015) as the previous study. However, cognition was used as their primary variable of interest in their predictive

models with assessment of cognitive status at baseline and 1-year follow-up. This study had a smaller sample size (113 at baseline and 79 at 1-year) but remained predominantly non-affective FEP (93%) confirmed by the SCID at 1-year follow-up. This sample had a mean age of 25.3, was 78% male, and had average DUP of 79 weeks. In this cohort, academic premorbid functioning was a significant independent predictor of both occupational outcome and disability use at 1-year follow up. In the multiple regression analyses, no cognitive measures improved models that included educational attainment or premorbid academic functioning. The premorbid social domain was not correlated with the cognitive variables or outcomes and therefore not included in the multivariate regression analyses. Strengths of this study are similar to described above (Ross M G Norman et al., 2015). The limitations include a smaller sample included here due to cognitive assessments and failure to report statistical analyses beyond the correlations as the models including the primary variables of interest, cognition, were not significantly improved.

Summary of Results using Premorbid Functional Domains

Ten reviewed studies from six cohorts investigated the PAS by using social or academic functional domains averaged across development. Of these, 8 found premorbid adjustment was associated with functional outcome. Study results are summarized in detail in Table 3.

Using regression models, three studies found social premorbid adjustment to be a significant, independent predictor of overall functional outcome (Ayesa-Arriola et al., 2013; Grau et al., 2016; R. M.G. Norman et al., 2012) throughout a range of follow-up periods including baseline, 1 year, 3 year, and 5 year. One additional study found premorbid social adjustment was an independent predictor of social functioning at study entry, near onset of the illness (Grau et al., 2016). An additional seven studies found social premorbid adjustment was associated with global and/or specific domains of functional outcome (global: 5, social: 2, occupational: 2, independent living: 1, disability: 1) (Albert et al., 2011;

Ayesa-Arriola et al., 2013; Barajas et al., 2013; Grau et al., 2016; Jeppesen et al., 2008; R. M.G. Norman et al., 2012; Simonsen et al., 2007).

In regression models, three studies found academic premorbid adjustment to be a significant, independent predictor of occupational functional outcome (Jeppesen et al., 2008; R. M.G. Norman et al., 2012; Ross M G Norman et al., 2015) over follow-up periods of baseline, 1 year, 2 year, and 5 years. An additional study found academic premorbid adjustment independently predicted disability use (Ross M G Norman et al., 2015) in a regression model. An additional five studies found academic premorbid adjustment was associated with overall and specific domains of functional outcomes (global: 2, social: 1, occupational: 4, disability: 1) (Albert et al., 2011; Ayesa-Arriola et al., 2013; Jeppesen et al., 2008; R. M.G. Norman et al., 2012; Ross M G Norman et al., 2015).

Using the consistent results from regression analyses, premorbid adjustment domains predict functional outcomes over the early course of illness as far as 5 years post diagnosis. Social premorbid adjustment appears to be a robust predictor of global functioning throughout the early stages of psychosis while academic premorbid adjustment is a replicated predictor of occupational functioning in particular.

Two studies from the same cohort (EASY, Hong Kong) did not find a relationship between premorbid adjustment domain and functional outcomes (Chang et al., 2016, 2018). These studies both investigated functional remission, a concept that requires lengthy duration and multiple criteria for remission, rather than functioning level at a given time point. This concept, while similar, may be different enough to explain the lack of identified relationship. Additionally, this cohort is older and in more chronic stages of illness than others reviewed here, which may also explain the lack of relationship when identified in all other included studies. One additional study did not identify a specific, independent relationship with premorbid adjustment and occupational outcomes in linear regression

models, but did find differences between social and academic premorbid adjustment in those that did and did not have a job at five year follow-up (Albert et al., 2011).

Premorbid Adjustment Developmental Periods

Since premorbid development is unlikely a static process in those who will go on to experience psychosis, investigating changes over the developmental periods of childhood, early adolescence, late adolescence, and adulthood is also important to explore. Studies which report this in the previous review find meaningful increases in effect sizes, particularly in adolescence, for prediction of negative symptoms and functioning (MacBeth & Gumley, 2008). Four studies were identified by the current review that reported at least one specific developmental period, and the findings will be reviewed below.

An additional study from the Hong Kong EASY cohort examined predictors of one-year follow-up functional outcomes (C. S.-Y. Chong et al., 2018). The sample included 77% non-affective psychosis patients with mean DUP of 25 weeks with 269 at baseline, 173 at 6-month, and 112 at 1-year follow-up. The sample was unusual compared to other early psychosis samples as only 35% were male and the average age was much higher than usual at 34 years of age. The criteria for entry as a first episode patient were described as the same as the previous EASY studies, but no use of the SCID to confirm diagnoses was mentioned, only DSM-IV criteria. Global functioning was measured with two scales, the SOFAS and RFS, at each time point. Every developmental time point excluding adulthood for premorbid adjustment was included. At baseline, premorbid adjustment during late adolescence was negatively correlated with global functioning, such that better adolescent premorbid adjustment (lower scores) was associated with better global functioning ($r = -0.17, p < 0.05$). At 6-month follow-up, both early (RFS: $r = -0.23, p < 0.01$; SOFAS: $r = -0.22, p < 0.05$) and late adolescence (RFS: $r = -0.30, p < 0.01$; SOFAS: $r = -0.28, p < 0.01$) were negatively correlated with global functioning, from RFS and SOFAS. Late adolescence was negatively correlated with 1-year RFS scores ($r = -0.30, p < 0.01$) but not SOFAS scores.

Despite the significant correlations, no developmental time point of the PAS was found as a significant predictor in regression models (C. S.-Y. Chong et al., 2018). Strengths of this study include the longitudinal design and use of developmental stages of premorbid adjustment. Limitations include high attrition from baseline which limits the generalizability of the findings and lack of investigation of subscales of functioning from the RFS. Additionally, this cohort included an older, mostly female sample which is unusual in early psychosis and was collected through a random assignment clinical trial of different length and provision of clinical services which could impact patient functional trajectories.

Two studies from the Spanish PAFIP research group reported developmental time periods of the PAS as predictors of outcome in early psychosis patients within their randomized, medication trial setting (Canal-Rivero et al., 2019; Pelayo-Terán et al., 2018). The first included a small sample of 65 first episode psychosis patients with the goal of examining predictors of 1-year functional outcome in domains of global, self-care, occupational, social, and family disability as measured by the DAS (Canal-Rivero et al., 2019). The majority of patients were diagnosed with a non-affective psychosis (86%) confirmed by the SCID for DSM-IV, but a small number met criteria for affective psychosis. This sample had a mean age of 26, were 68% male, and reported an unusually short mean DUP of 0.57 weeks. The PAS scores were averaged, regardless of domain, for each development stage excluding adulthood. Findings illustrated a strong relationship with late adolescence as it was correlated with occupational disability, family disability, social disability, and overall disability. Late adolescent premorbid adjustment was also an independent predictor of social disability ($B = 0.08$, $t = 2.74$, $p = 0.02$, $CI[0.02-0.15]$), and when looking at just the non-affective sample, late adolescence was the sole predictor of overall disability ($B = 0.26$, $t = 2.76$, $p < 0.01$, $CI [0.07-0.45]$) (Canal-Rivero et al., 2019). Childhood and early adolescence were not predictors of any outcome domain. Strengths of this study included the longitudinal design and multiple functional outcomes reported. The sample size was quite small

especially considering the larger PAFIP study has a much larger cohort, the patients were recruited as part of a medication trial, and numerous multiple regression models were conducted.

The second study from the PAFIP group included 307 non-affective early psychosis patients and investigated the effects of duration of active psychosis after beginning treatment and duration of untreated psychosis on three-year functioning and functional recovery (Pelayo-Terán et al., 2018). Diagnoses were confirmed with the SCID for DSM-IV 6 months after study entry. Patients met criteria for study inclusion if they had fewer than 6 weeks of antipsychotic treatment and were deemed to be in their first episode of psychosis. The sample had a higher than average mean age of 30, 55% male, and mean DUP of 54 weeks. Functional outcomes were measured with the same scale as in the previous study, the DAS, but groups were created based on good and poor functioning from the global evaluation item where a zero or one was good functioning and a score above one was poor. Recovery groups were determined based on occupational status (current engagement in at least part-time school or work considered in recovery) and minimal disability (0 or 1 on DAS). All developmental time points, the general subscale, and an overall average of the PAS were used. Patients who met the functional recovery (124, 40%) criteria versus those who did not (183, 60%) had significantly better PAS development period scores except for adulthood which did not differ (including overall and general scale). The good overall functioning group also had significantly better PAS developmental subscales scores than the poor group, with one exception. The adulthood score was slightly worse in the good functioning group (N = 180, 59%) compared to the poor functioning group (N = 126, 41%), although this stage is commonly excluded from analyses due to concerns of its overlap with prodrome or onset of psychosis. Average overall premorbid adjustment was a significant predictor of both general functioning (Wald = 11.72, $p < 0.001$) and functional recovery (Wald = 10.08, $p < 0.001$) in logistic regression models, but developmental periods of the PAS were not included in these models despite significant differences between groups (Pelayo-Terán et al., 2018). This limits our understanding of the developmental stages

of premorbid adjustment predicting post-illness functioning. The longitudinal design with long term follow-up and large sample size were strengths of this study. Limitations include the general use of the PAS and functional outcomes and study enrollment of a clinical trial setting that could have differing effects on outcome.

A final study from the Dublin and East Treatment and Early Care Team (DETECT) cohort in Ireland investigated 4- and 8-year symptomatic and functional outcomes in 118 non-affective first episode psychosis patients in a prospective, naturalistic study setting (Crumlish et al., 2009). Diagnoses were confirmed with the SCID for DSM-IV and patients were included if presenting for their first episode of psychosis or duration of treatment with anti-psychotics was less than 30 days. This sample had a mean age of 26.9, was 61% male, and mean DUP of 24.5 weeks. Functioning was measured with the GAF-F, Specific Levels of Functioning (SLOF), and the Quality of Life Scale (QLS). Childhood premorbid social functioning was the sole measure from the PAS used in analyses as authors felt that the adolescence stage was too close to the prodromal or active psychosis period. They provided no explanation on which items were included in this constructed variable or why academic functioning would have been left out. However, since they title the variable, Premorbid Social Adjustment ages 5-11, it is assumed that the first two, social items are the only ones included in this variable (withdrawal, peers). Although this does not provide information about developmental change of functioning over time, the childhood functioning itself is still of interest for this review. This measure was associated with 8-year GAF-F scores and included in the linear regression model, however, it was not a significant, independent predictor of 8-year functioning (Crumlish et al., 2009). Strengths of this study include the purely non-affective psychosis cohort, prospective, longitudinal, and naturalistic study design with long-term follow-up. Limitations include most of the PAS data being ignored, the full sample did not have data on this scale at all (missing for 20 of 118), high attrition rate of 43%, and use of the GAF-F which is a limited measurement scale. Detailed results for all fourteen studies are reported in Table 1.3.

Table 1.3. Summary of Systematic Review Results

Cohort	Time Points	Sample Size	Functional Outcome Domain	Functional Outcome Scale	PAS Predictor	Regression Statistic				Univariate Statistic				
						Social	Occ	Ind Liv	Global	Social	Occ	Ind Liv	Global	
Barajas, 2013; GENIPE	Baseline	33	G	DAS, LSP	Social									
					Academic									DAS: r=0.38* LSP: r=-0.46* DAS: NS LSP: NS
Grau, 2016; GENIPE	Baseline	90	G, O, S, IL	DAS	Social	B=2.10*	NS	NS	B=4.57*	r=0.42*	NS	r=0.39*	r=0.41*	
					Academic	NT	NT	NT	NT	NS	NS	NS	NS	
Simonsen, 2007; TIPS	Baseline, 3 mon, 1yr	298; 280; 266	G	GAF-F	Social (child)				R ² =0.21*					
					Academic				NS					
Ayesa-Arriola, 2013; TIPS	Baseline, 1yr, 3yr	284; 222; 202	G	DAS	Social (1yr)				B=0.64*				u=345*	
					Academic (1 yr)				NT				t=-3.90*	
					Social (3 yr)				B=0.45*				u=3.11*	
					Academic (3 yr)				NT				t=-3.84*	
Jeppesen, 2008; OPUS	Baseline, 1yr, 2yr	423; 334; 294	O, S	SNS	Social (baseline)	NR*				r=-0.37*	NT			
					Social (1 yr)	NR*				r=-0.27*	r=-0.11*			
					Social (2 yr)					r=-0.23*	r=-0.03			
					Academic (baseline)					r=-0.18*	NT			
					Academic (1 yr)		NR*			r=-0.12*	r=-0.16*			
					Academic (2yr)		NR*			r=-0.15*	r=-0.15*			
Albert, 2011; OPUS	Baseline; 5 yr	468; 255	O	Work Status, no scale	Social	NT	NS	NT	NT	NT	OR Exp(B) CI=0.81*	NT	NT	
					Academic	NT	NS	NT	NT	NT	OR Exp(B) CI=0.85*	NT	NT	

Table 1.3 Continued

Cohort	Time Points	Sample Size	Functional Outcome Domain	Functional Outcome Scale	PAS Predictor	Regression Statistic				Univariate Statistic			
						Social	Occ	Ind Liv	Global	Social	Occ	Ind Liv	Global
Chang, 2016; <i>EASY</i>	Baseline, 6 mon, 1 yr	156	FR	SOFAS, RFS	Social					NT	NT	NT	NS
					Academic					NT	NT	NT	NS
Chang, 2018; <i>EASY</i>	Baseline, 3 yr	143	FR	SOFAS, RFS	Social					NT	NT	NT	NS
					Academic					NT	NT	NT	NS
Norman, 2012; <i>PEPP</i>	Baseline, 5 yr	132	G, O	SOFAS, LCS	Social	NS	NS	NS	$\beta=-0.18^*$	NT	NS	NT	$r=-0.25^*$
					Academic	NS	NS	NS	NS	NT	$r=-0.20^*$	NT	NS
Norman, 2015; <i>PEPP</i>	Baseline, 5 yr	113; 79	G, O, IL	SOFAS, LCS	Social	NT	NT	NT	NT	NT	FT work: $r=-0.24^*$ Wks FT: $r=-0.20^*$	NT	$r=0.18^*$
					Academic	NT	NR*	NT	NT	NT	NT	FT work: $r=-0.24^*$ Wks FT: $r=-0.20^*$	NT
Canal-Rivero, 2018; <i>PAFIB</i>	Baseline, 1 yr	65	G, O, S, IL	DAS	Child	NT	NT	NT	NT	NS	NS	NS	NS
					Early Ad	NT	NT	NT	NT	NS	NS	NS	NS
					Late Ad	$B=0.08^*$	NS	NT	$B=0.26^*$	$r=0.41^*$	$r=0.31^*$	NS	$r=0.38^*$
					Adult	NT	NT	NT	NT	NT	NT	NT	NT
Pelayo-Teran, 2018; <i>PAFIB</i>	Baseline, 3 yr	415; 307	G, O, FR	DAS	Child					NT	$t=-3.42^*$	NT	$t=-3.32^*$
					Early Ad					NT	$t=-5.64^*$	NT	$t=-5.54^*$
					Late Ad					NT	$t=-5.75^*$	NT	$t=-5.99^*$
					Adult					NT	NS	NT	$t=-3.01^*$

Table 1.3 Continued

Cohort	Time Points	Sample Size	Functional Outcome Domain	Functional Outcome Scale	PAS Predictor	Regression Statistic				Univariate Statistic			
						Social	Occ	Ind Liv	Global	Social	Occ	Ind Liv	Global
Chong, 2018; <i>EASY</i>	Baseline, 6 mon, 1 yr	269; 173; 112	G	SOFAS, RFS	Child (baseline)				NT				NS
					Early Ad (baseline)				NT			NS	
					Late Ad (baseline)				NS			SOFAS: NS RFS: $r=-0.17^*$	
					Adult (baseline)				NT			NT	
					Child (6 mon)				NT			NS	
					Early Ad (6 mon)				NS			SOFAS: $r=-0.22^*$ RFS: $r=0.23^*$ SOFAS: $r=-0.28^*$ RFS: $r=-0.30^*$	
					Late Ad (6 mon)				NS			NS	
					Adult (6 mon)				NT			NT	
					Child (6 mon)				NT			NS	
					Early Ad (1 yr)				NT			NS	
					Late Ad (1 yr)				NT			NS	
Adult (1 yr)				NT			NT						
Crumlish, 2009; <i>DETECT</i>	Baseline; 4 yr; 8 yr	118; 67	G	SLOF, QLS	Child				NS				$r=NR^*$
					Early Ad							NT	
					Late Ad							NT	
					Adult							NT	

* $p<0.05$; NT = not tested, NS = not significant; NR = Not reported; G = Global, O/Occ = Occupational, S = Social, IL = Independent Living, FR = Functional Recovery

Summary of Results using Premorbid Developmental Periods

Four reviewed studies from three cohorts investigated the PAS used averaged scores within each developmental stage regardless of functional domain. Of these, three found the PAS development stages were associated with functional outcomes, and one did not report correlations. Using regression models, one study found late adolescent functioning to be a significant, independent predictor of both social and overall functional outcome (Canal-Rivero et al., 2019) at one year follow-up. A second study included group differences for each PAS development stage but only included the global PAS score in regression models, so these findings will not be reviewed in this paper (Pelayo-Terán et al., 2018). Two other studies did not find PAS development stages to be significant independent predictors of functional outcome in regression models (C. S.-Y. Chong et al., 2018; Crumlish et al., 2009).

The three studies reporting correlations between PAS development stages and functional outcomes all found significant relationships. Childhood premorbid adjustment was associated with functioning in two studies: 1) childhood social functioning was correlated with 8-year GAF-F (Crumlish et al., 2009), and 2) better childhood premorbid adjustment scores were found in patients who met three-year functional recovery and classified as good functioning than in those that did not (Pelayo-Terán et al., 2018). Early adolescence premorbid adjustment was associated with 6 month functional outcomes (C. S.-Y. Chong et al., 2018), and different between functional recovery and functioning groups at 3-year follow-up (Pelayo-Terán et al., 2018). Late adolescent premorbid adjustment was significantly associated with baseline, 6-month, and 1-year global functioning (C. S.-Y. Chong et al., 2018), and 1-year occupational, social, and global functioning (Canal-Rivero et al., 2019). Late adolescent functioning was also different between three-year functional recovery (in recovery vs. not in recovery) and functioning groups (good vs. poor functioning) (Pelayo-Terán et al., 2018). Adulthood premorbid adjustment was different between current three-year functioning groups but not more sustained functional recovery

groups (Pelayo-Terán et al., 2018). A brief summary of results and study characteristics and criticisms is included in Table 1.4.

Discussion

Summary of Results

Fourteen studies investigated how specific sub-components of pre-illness functioning, are related to post-illness psychosocial outcomes in early psychosis. Pre-illness functioning as measured by the PAS was investigated in two primary ways: domain of functioning of academic and social adjustment (10 studies) and functioning developmental stage including childhood, early and late adolescence, and early adulthood (4 studies). Psychosocial outcomes included in this review were improved from a previous review by including only objective rating scales that solely measured functioning without confounding active psychosis symptoms in the ratings.

Premorbid Functional Domains

Eight of the ten studies that used functional domains of the PAS found an association with post-diagnosis psychosocial outcome at various longitudinal follow-ups of up to five years. Consistent findings from regression models support the use of splitting premorbid adjustment data by domain of pre-illness functioning with investigations of both social and academic functioning separately. Social premorbid adjustment was a significant, independent predictor of post-diagnosis global psychosocial outcome and social functioning specifically (Ayesa-Arriola et al., 2013; Grau et al., 2016; R. M.G. Norman et al., 2012). Academic premorbid adjustment was a significant, independent predictor of occupational outcome up to five years from study entry (Jeppesen et al., 2008; R. M.G. Norman et al., 2012; Ross M G Norman et al., 2015). Many other studies did not use the most robust method of including domains of pre-illness functioning in regression prediction models, instead exploring univariate associations or group differences. These findings also support the robust relationship of pre-illness functional domains and

Table 1.4. Brief Summary of Systematic Review Included Samples, Results, and Criticisms

Study; Cohort	Analysis Time Points	Sample Size	Mean Age; %Male	PAS Variables	Functional Outcome Variable	Main Result
Domain Approach						
Barajas, 2013; <i>GENIPE</i>	Baseline	33	26.1; 61%	Social Academic	G	+ Correlation: PAS-S with G PAS-A with G
<i>Primary Study Criticisms:</i> Small Sample; No Follow-up; Limited Outcome variables; Adulthood excluded; No standardized diagnostic assessment completed						
Grau, 2016; <i>GENIPE</i>	Baseline	90	20.6; 59%	Social	G, O, S, IL	Regression: PAS-S on G
<i>Primary Study Criticisms:</i> No follow-up; Academic PA Missing						
Simonsen, 2007; <i>TIPS</i>	Baseline, 3 mon, 1yr	298; 280; 266	27.8; 58%	Social (child) Academic	G	Regression: PAS-S on G
<i>Primary Study Criticisms:</i> Older sample; Limited Outcome variables; Only childhood Social PA included; No follow-up Dx						
Ayasa-Arriola, 2013; <i>TIPS</i>	Baseline, 1yr, 3yr	284; 222; 202	29; 57%	Social Academic	G	Regression: PAS-S on G at 1yr PAS-S on G at 3yr
<i>Primary Study Criticisms:</i> Older sample; Limited Outcome variables; PAS-A left out of Reg despite significant correlations; Sample within clinical trial setting; Diagnosis not confirmed at 3 year visit						
Jeppesen, 2008; <i>OPUS</i>	Baseline, 1yr, 2yr	423; 334; 294	26; 56%	Social Academic	S, O	Regression: PAS-S on S (base, 1yr) PAS-A on O (1yr, 2yr)
<i>Primary Study Criticisms:</i> Adulthood excluded; Sample within clinical trial setting; Occupational functioning not measured with standardized scale; Diagnosis not confirmed at 2 year visit						
Albert, 2011; <i>OPUS</i>	Baseline; 5yr	468; 255	26; 56%	Social Academic	O	Odds Ratio: PAS-S and O PAS-A and O
<i>Primary Study Criticisms:</i> Limited Outcome variables; Adulthood excluded; Sample within clinical trial setting; Occupational functioning not measured with standardized scale; Diagnosis not confirmed at 2 year visit; Long mean DUP						
Chang, 2016; <i>EASY</i>	Baseline, 6 mon, 1 yr	156	22.9; 52%	Social Academic	FR	Not Sig
<i>Primary Study Criticisms:</i> Limited Outcome variables; More stringent outcome variable; Enrolled after a 2 yr clinical trial						
Chang, 2018; <i>EASY</i>	Baseline, 3 yr	143	22.9, 52%	Social Academic	FR	Not Sig
<i>Primary Study Criticisms:</i> Limited Outcome variables; More stringent outcome variable; Enrolled after a 2 yr clinical trial						
Norman, 2012; <i>PEPP</i>	Baseline, 5 yr	132	23.8; 77%	Social Academic	G, O	Regression: PAS-S on G
<i>Primary Study Criticisms:</i> No 5 yr diagnostic confirmation; overrepresentation of males						
Norman, 2015; <i>PEPP</i>	Baseline, 5 yr	113, 79	25.3; 78%	Social Academic	G, O, IL	Regression: PAS-A on O
<i>Primary Study Criticisms:</i> No 5 yr diagnostic confirmation; overrepresentation of males; Statistical data not reported only described.						

Table 1.4 Continued

Study; Cohort	Analysis Time Points	Sample Size	Mean Age; %Male	PAS Variables	Functional Outcome Variable	Main Result
Developmental Approach						
Canal-Rivero, 2018; <i>PAFIB</i>	Baseline, 1 yr	65	26; 68%	Child Early Ad Late Ad	G, O, S, IL	Regression: PAS-LA on S PAS-LA on G
<i>Primary Study Criticisms:</i> Adulthood PA missing; Small sample; Unusually short DUP; Within Clinical Trial						
Pelayo-Teran, 2018; <i>PABIF</i>	Baseline, 3 yr	415; 307	30; 55%	Child Early Ad Late Ad Adult	G, O	Group Differences (by G and O status): G: PAS-C, EA, & LA O: PAS-C, EA, LA, & AD
<i>Primary Study Criticisms:</i> Regression model limited to mean PAS; Adulthood PA; Older sample; Within Clinical Trial						
Chong, 2018; <i>EASY</i>	Baseline, 6 mon, 1 yr	269; 173; 112	34.2; 35%	Child Early Ad Late Ad	G	- Correlation: PAS-EA with G (6 mon) PAS-LA with G (base, 6 mon)
<i>Primary Study Criticisms:</i> Adulthood period missing; Limited Outcome variables; Older sample, predominantly female; High loss to follow-up; Lack of structured diagnostic assessment to confirm diagnoses; High attrition over 1 year follow-up; Enrolled after a 2 yr clinical trial; No standardized diagnostic assessment completed						
Crumlish, 2009; <i>DETECT</i>	Baseline, 4 yr, 8 yr	118; 67	26.9; 61%	Child	G	Correlation: PAS-C with G
<i>Primary Study Criticisms:</i> Single developmental period included; Limited Outcome variables; PAS data missing for 20 subjects; High attrition over the long follow-up period						

Mon = months, Yr = year, Base = Baseline; PAS = Premorbid Adjustment Scale; Functional Outcome Variable abbreviations include: G = Global, O = Occupational, S = Social, IL = Independent Living Skills, FR = Functional Recovery; PAS-S = PAS social subscale, PAS-A = PAS academic subscale, Premorbid Developmental Time Periods are abbreviated as: Child, C = Childhood, Early AD, EA = Early Adolescence, Late Ad, LA = Late Adolescence, Adult, A = Adulthood

post-illness psychosocial outcomes at various follow-ups (Albert et al., 2011; Ayesa-Arriola et al., 2013; Barajas et al., 2013; Grau et al., 2016; Jeppesen et al., 2008; R. M.G. Norman et al., 2012; Ross M G Norman et al., 2015; Simonsen et al., 2007). Just two studies from the same cohort (EASY; Hong Kong) did not find significant relationships between premorbid functional domains and post-illness psychosocial outcomes (Chang et al., 2016, 2018). These studies examined a more stringent functional remission concept, and the sample was much older and further into the illness which may explain the lack of significant relationship.

Bringing these findings together, consistent results from regression analyses demonstrate the value of examining premorbid functional domains in predicting post-illness psychosocial functioning as far as 5 years following initial diagnosis. Social premorbid adjustment appears to be a robust predictor of global functioning throughout the early stages of psychosis while academic premorbid adjustment is a replicated predictor of occupational functioning in particular. Despite the EASY cohort's negative findings and inconsistent reporting of both domains in all studies, a consistent effect is demonstrated across the majority of studies supporting the contention that domain specific separation of pre-illness functioning is a robust predictor of future psychosocial outcomes in early stage psychosis.

Premorbid Developmental Stage

Four reviewed studies from three cohorts investigated the PAS by using averaged scores within developmental stages, regardless of functional domain. Regression models presented mixed findings related to development stage as an independent predictor of psychosocial outcomes. One study found late adolescent functioning to be a significant, independent predictor of both social and overall functional outcome at one year follow-up, while two other studies did not find significant relationships (Canal-Rivero et al., 2019; C. S.-Y. Chong et al., 2018; Crumlish et al., 2009). Bivariate relationships provided more consistent associations between functioning at a specific developmental stage and post-illness psychosocial outcomes. One study identified significantly better premorbid adjustment scores for

patients in functional recovery at three year follow-up compared to those who were not in functional recovery at all developmental stages (Pelayo-Terán et al., 2018). Childhood premorbid adjustment was correlated to 8-year global functioning (Crumlish et al., 2009). Early adolescence premorbid adjustment was associated with 6 month post-illness global functional outcome (C. S.-Y. Chong et al., 2018). Late adolescent premorbid adjustment was significantly associated with baseline, 6-month, and 1-year global functioning, and 1-year occupational, social, and global functioning (Canal-Rivero et al., 2019; C. S.-Y. Chong et al., 2018). These developmental findings support the conclusions from the previous MacBeth & Gumley review and reiterate the need to explore premorbid adjustment across development stages, beyond an overall average (MacBeth & Gumley, 2008).

Together, these results illustrate a consistent association between both the domains of premorbid adjustment and the trajectory across development for predicting later, post-illness psychosocial outcomes. These results provide important information that suggest how an individual performs in their environment before the illness presents itself, can be a useful prognostic indicator for functional strengths and challenges which may be helpful in preventative and intervention strategies. These targeted interventions, both before and after illness onset, may help promote psychosocial recovery.

Critiques of included studies

Critiques of PAS use

Both methods of using PAS data (functional domain, developmental period) have particular appeal, but each leave out potentially important information. Importantly, no study was identified in this systematic review that used a comprehensive approach including both functional domain and developmental time period together in the same analysis.

The functional domain approach uses separate academic and social functioning scores, averaged across development stage, which are likely to be related to specific occupational or social outcomes

post-diagnosis. However, meaningful information about how these domains may change over time is not represented through this approach. Many studies included only one of these domains in their regression models for concerns about collinearity. These decisions, especially when made without data to support collinearity issues, limit the ability to discuss premorbid adjustment as a whole or make claims about which premorbid functional domain may have the best predictive power for specific areas of post-illness functioning.

The developmental method allows investigation of change over time, which has particular prognostic relevance in patients who ultimately develop a psychotic disorder (Kelley et al., 1992; Rabinowitz et al., 2000). However, while this approach provides developmental data, information specific to domain of functioning, is lost. Unfortunately, studies included in this review using a developmental approach were limited to four; one of which only used childhood functioning and one which ultimately used an overall score in regression models despite significant differences across development stage (Crumlish et al., 2009; Pelayo-Terán et al., 2018). An additional criticism to this method is that most groups do not utilize the full developmental course for various, often non-specified, reasons. Only one developmental PAS paper included the adulthood period which is a significant limitation of this section. The psychosocial outcome measures included were limited in scope, as only one paper included domains of functioning beyond a global score, and this study did report significant relationships for both social and occupational functioning (Canal-Rivero et al., 2019). These issues illustrate a limited examination of premorbid developmental trajectories in the current review.

Broad Critiques across Included Studies

The use of the PAS was varied and not always clearly defined in studies included in this review. The scale is constructed to include up to one year prior to the onset of psychosis to both capture the full premorbid period and exclude early phases of the illness or prodrome that may artificially show a decline in premorbid adjustment. Despite this consideration in instructions for use of the scale, many

studies make a blanket decision to only include certain early development periods, most commonly childhood and early adolescence. This limits the information for patients with later onsets, even for the development stages before or during common onset times of 18 to 25 (Kessler et al., 2007). While this technique is used as a conservative tactic to avoid including onset of illness related decline in measures of premorbid adjustment, it is likely that valuable information of the full developmental trajectory of functioning will be lost for those with standard or later onsets.

A final criticism is the lack of consensus on post-diagnosis functioning measures used throughout included studies. There are no clearly preferred psychosocial outcome measures making comparison across studies difficult. Many groups utilize the GAF-F which is a very simplistic, rough measure without a thorough interview or scoring guide that provides a global score, ignoring the domains of functioning. It is likely that social versus occupational functioning are different for patients and associated with differing factors. Use of global measures of functioning limits specificity of findings. Examining social and occupational outcomes separately within the same samples was rare in the reviewed studies—only 2 of 10 in functional domain studies and 1 of 4 in developmental studies. This would provide a more thorough understanding of specific areas of functioning that are likely to differ from one another. These differences highlight individuals' strengths and challenges which is important for intervention efforts targeting psychosocial recovery in specific domains.

Limitations of this review

This review was not completed without limitations. First, due to the significant heterogeneity across studies in use of PAS and functioning measures, these findings are difficult to quantitatively assess, as in a meta-analytic approach, which has not been carried out thus far. Second, differing clinical definitions and inclusion criteria across studies is a caveat for these results. Many studies included both affective and non-affective psychosis, despite these groups having different outcomes (Bora, 2016). None of these studies clearly described the length of psychosis despite defining their samples as early.

This is a broad issue in the field that does make it difficult to compare findings across groups. Some early psychosis samples include patients with up to five years of illness at study entry while others limit this at one-year (Newton et al., 2018). It is clear that the length of psychosis may greatly impact psychosocial outcomes. Finally, despite investigations in large samples (300+), there have been minimal exploration of how race or ethnicity may impact scores on this scale. Although previous reports have shown no differences across gender with the PAS, most groups do not report data by gender, race, or ethnicity (Krauss et al., 1998; Tor K. Larsen, McGlashan, Johannessen, & Vlbe-Hansen, 1996).

Conclusions

The PAS is a robust predictor of psychosocial outcomes in early psychosis across numerous investigations. Both investigations of separate functional domains of academic and social pre-illness functioning and premorbid adjustment across developmental stages before the onset of psychosis, show associations with global and specific domains of psychosocial functioning. Unfortunately, no study has yet to separately examine functional domains by developmental trajectory in a complete analysis as it relates to specific post-illness psychosocial domains. Because of the consistency of this relationship, a more comprehensive examination including social and academic functioning throughout development prior to the onset of psychosis, will likely provide important information for predicting psychosocial outcomes post-illness. The prognostic implications of further teasing out these predictive relationships, will be valuable for preventative and early intervention efforts for this highly disabling condition. The ability to tailor social and educational or occupational and cognitive interventions to areas of individual patient strengths and challenges will likely bolster functional recovery efforts for patients with psychosis. The implications are encouraging as disability rates and duration are often life-long in this disorder despite clinical symptoms often reducing or even remitting throughout the illness.

Future Directions

Results from this review and previous reports of PAS and psychosocial functioning are difficult to compare across various methods of PAS use, clinical samples, and psychosocial outcomes included. With a previous systematic review from 2008 and an update to the literature including more details of psychosocial domains included, a meaningful and logical next step to quantify the strength of these relationships would be a meta-analysis. Examining the strength of various PAS approaches on separate dimensions of psychosocial functioning would improve the strength of conclusions about this relationship. As no meta-analysis has examined this relationship previously, this would be an important next step in this line of research.

Investigations using the PAS to explore the contributions of gender, race, and ethnicity, especially from an intersectional lens are lacking in the current literature. We know these demographic factors create different experiences and outcomes in society in numerous ways, and specifically, female gender is commonly associated with minimally better outcomes in the early stages of schizophrenia (Seeman, 2019). Future investigations which put these important demographic factors at the forefront in investigations of premorbid adjustment and psychosocial outcomes may provide crucial information for better understanding these patterns of individual differences. This would be an important undertaking in future studies.

Another important future direction from this work is to complete a study that utilizes a comprehensive approach examining domain of functioning throughout the pre-illness course as it relates to psychosocial functioning in early psychosis. No study included in the current or previous review has comprehensively used this information to predict later social and educational/occupational functioning across the course of illness. Many previous studies included methodological limitations which, if addressed, would strength understandings of these relationships. If specific trajectories of pre-illness domain functioning leads to a better understanding of post-illness functioning, these potentially

modifiable behaviors may be better understood and targeted with prevention and intervention efforts.

A comprehensive approach is the best next step to fully test these relationships and learn more information relevant to prognosis of psychotic disorders from pre-illness and early stages.

CHAPTER II

PREMORBID FUNCTIONING PATTERNS AND POST-ILLNESS PSYCHOSOCIAL

FUNCTIONING IN THE EARLY STAGES OF PSYCHOSIS

Abstract

Psychosis, and schizophrenia in particular, presents with debilitating symptoms and impaired cognition and psychosocial functioning. Severe psychosocial functioning impairments are seen even despite resolution of psychotic symptoms and are not well understood. Premorbid adjustment, or the developmental performance prior to the initial psychotic episode, is a robust prognostic indicator for many clinical outcomes in psychosis. This investigation set out to explore the relationships of pre-illness social and academic performance to post-onset psychosocial functioning in the early stages of psychosis, within two years of the onset of psychotic illness. One hundred and four non-affective early psychosis patients were assessed for psychiatric diagnoses, premorbid functioning using the PAS, and post-onset psychosocial functioning using the Personal and Social Performance scale (PSP) and Quality of Life Scale (QLS). Four variables were created to characterize the premorbid period using trajectory over development and domain of functioning: social and academic intercept (initial starting level), social and academic slope (change in performance over development). Global psychosocial functioning was operationalized as the 0 to 100 score from the PSP and social and occupational functioning scores were created from sub-scales of the QLS. Relationships between premorbid variables and post-onset psychosocial functioning for social, occupational, and global functioning were analyzed with linear regression models. Post-onset global psychosocial functioning at study entry was significantly predicted by the premorbid change in social performance over time and the initial academic level in childhood. Post-onset social functioning was significantly associated with both the premorbid initial starting level and change over time for social performance. Occupational functioning at study entry was not significantly predicted by any premorbid variables. Our findings illustrate the importance of social and academic premorbid adjustment in relationship to subsequent functional ability after the presentation of psychosis at study entry. This information may be useful in creating individualized psychosocial interventions based upon the foundational pre-illness functional information to best support

psychosocial recovery in psychotic disorders. Future investigations should focus on establishing a longitudinal prediction of functioning at more distal follow-up along the course of psychosis to bolster support for this method and future intervention efforts in early psychosis.

Introduction

Schizophrenia is a severe and persistent mental illness with a high burden of disability despite largely successful pharmacologic treatment for psychotic symptoms (Fusar-Poli et al., 2017). Despite this, schizophrenia is a highly heterogeneous disorder with a variety of disease courses and outcomes (Ciompi, 1980). Investigations targeting understanding pathways to severe, negative outcomes from psychosis versus remission and recovery are very important to lessening the burden experienced by this severe and persistent mental illness. Current understandings of schizophrenia following the critical period hypothesis, postulate that the major impairment and severe decline in functioning seen in chronic schizophrenia occurs in the early stages (Birchwood et al., 1998). This theory states that the first two to five years after the onset of psychosis are the most important for intervention efforts due to a declining process caused by untreated psychosis that settles into a more permanent state after the early stages of schizophrenia (Birchwood et al., 1998). Therefore, characterizing and closely following patients as soon as the initial psychotic episode presents, is imperative to understanding the disease progression particularly with changing the trajectory to more positive outcomes and recovery.

Psychosocial functioning represents an individual's ability to operate successfully and healthily in society. Psychosocial functioning can be measured in different ways including self-report, objective interviewer rated, and functional capacity which measures based on demonstration of abilities. Objective interviewer rated methods focus on what the patient is doing, regardless of what they may be able to do, as this represents the real life functioning of the patient. Psychosocial functioning can be operationalized as global or overall functioning or broken into sub-parts of functioning, the most important being social and occupational performance. Psychosocial functioning deficits in schizophrenia are not highly correlated with active psychotic symptoms, cognition, or other disease outcomes but are responsible for the serious disability seen in psychosis (Alvarez-Jimenez et al., 2012; William T.

Carpenter & Strauss, 1991; Michael Foster Green, 1996; Michael Foster Green et al., 2000; Harvey & Strassnig, 2012).

One area of interest that may best inform post-onset psychosocial functioning is the developmental or premorbid functioning prior to the onset of psychosis. Premorbid functioning represents an individual's ability to successfully function socially and academically throughout development from childhood until late adolescence or early adulthood when psychosis typically emerges. Premorbid functioning is informative about an individual's strengths and difficulties prior to the disruptive illness process. Premorbid functioning has been linked to numerous outcomes in schizophrenia, but psychosocial functioning has not received a lot of interest over clinical outcomes (MacBeth & Gumley, 2008; Malla & Payne, 2005; McGlashan, 2008; Van Mastrigt & Addington, 2002). The small amount of studies that have investigated these relationships consistently demonstrate moderate associations particularly for premorbid social performance and functioning during late adolescence, mainly with global functioning (Haas & Sweeney, 1992; T. K. Larsen et al., 2004; MacBeth & Gumley, 2008). Social premorbid functioning and post-onset social functioning after the initial psychotic episode has also been described (Jeppesen et al., 2008).

Studies who have explored these relationships consistently find small to moderate effect sizes but have methodological concerns that may be improved upon. Many studies that investigate these relationships use broad averages by domain of functioning or at each development stage which limits a comprehensive understanding of the premorbid patterns. Using either a domain approach or a developmental stage approach is collapsing potentially important information of domain by development. The majority of identified studies in the literature examined overall functioning which limits our understanding of different areas of functioning such as occupational or social functioning. In the current study, we plan to improve upon previous studies in this area by using a comprehensive approach to the PAS defining an initial starting level and trajectory over the premorbid period for both

social and academic premorbid functioning. We also are investigating social and occupational post-onset functioning in addition to global functioning, in a well characterized purely non-affective psychosis sample. We anticipate, with methodological improvements, that premorbid social initial level and trajectory will be related to post-onset social functioning. Similarly we anticipate that premorbid academic variables will predict post-onset occupational functioning. As global functioning as elements of the previous outcomes, we anticipate all premorbid variables to be associated with post-onset global functioning.

Methods

Research Design

The design of this research was a prospective, longitudinal study that followed early psychosis patients over the course of two years from study enrollment. We allowed for study enrollment to occur within the first two years of illness and then followed patients for the next two years from the baseline visit. This design was chosen to allow for investigation of outcomes soon after an initial episode of psychosis and to follow patients over time to track illness progression and distal outcomes, as they may change from baseline. Upon study entry, subjects underwent an initial diagnostic interview research visit to collect diagnostic, premorbid adjustment, and initial post-onset psychosocial functioning assessments. All assessments were conducted by a clinician with the subject, and all available medical records were obtained and reviewed for relevant information for scoring purposes. In this paper, baseline or study entry results are presented.

Subjects

Patient Identification and Recruitment

The population of focus for the research was patients with early-stage psychosis. Subjects for the proposed research were recruited as part of a NIMH funded prospective, longitudinal early psychosis investigation (Grant No. R01-MH70560). Subjects were recruited from Vanderbilt University Medical

Center (VUMC) inpatient psychiatric hospital and outpatient clinics through routine daily screening of medical records and coordination with treatment providers. All non-affective psychosis patients who met inclusion/exclusion criteria, were approached in person on the unit or in the clinic or by phone by a member of the research team following permission by their treating physician. The two-year longitudinal study was explained and consent was obtained. Patients in this study were recruited as near to the onset of psychosis as possible. This was important for prospective investigations of changes over time due to a debilitating mental health disorder. Inclusionary criteria required that subjects: 1) were within two years of psychosis onset by the time of study enrollment; 2) met criteria for a non-affective psychotic disorder including brief psychotic disorder, schizophreniform disorder, schizophrenia, or schizoaffective disorder; 3) were between 16 and 40 years of age. Exclusionary criteria included: 1) history of a major medical (HIV, cancer, etc.) or neurological (Multiple Sclerosis, epilepsy, etc.) illness which may cause psychotic symptoms; 2) active substance use disorders in the past month, as these may cause psychosis; and 3) intellectual or developmental disorder.

Sample Characteristics

The sample included 104 early psychosis patients, recruited within the first two years since illness onset. The sample had a mean age of 23 (range: 16-39) with a standard deviation of 4.01. Gender of the sample was 77% male and 23% female. Racial make-up of the sample was 65% White, 32% Black, 2% Asian, and 1% Other. The baseline diagnostic summary of the sample included: 3% Brief Psychotic Disorder, 66% Schizophreniform Disorder, 8% Schizoaffective Disorder, and 23% Schizophrenia.

Data Collection

Diagnostic Interview

At study enrollment, subjects underwent a high quality, comprehensive semi-structured diagnostic interview with the Structured Clinical Interview (SCID) for DSM-IV-TR by a trained rater (First, M. B., Gibbon, R. L., Spitzer, R. L., Williams, 1995). The SCID is the gold standard in psychiatric research

with excellent reliability and takes roughly three to four hours to complete (Lobbestael, Leurgans, & Arntz, 2011). The interviewer used the structured interview to complete a comprehensive diagnostic review of psychiatric illnesses including mood, psychosis, substance use, anxiety, eating, trauma, and obsessive compulsive disorders. To supplement the patient's report, all medical record data (for VUMC and beyond) were obtained and included for objective information from treatment providers and informants to increase the accuracy of information. These records were especially helpful in determining the specific timing of onset and course of psychosis and particular psychotic symptoms that may be difficult for patients to report or recall. From this comprehensive information, a specific psychosis onset date was determined. This was crucial for diagnostic decisions in the early stages of psychosis to make determinations between brief psychosis (at least 1 day, less than one month), schizophreniform disorder (at least 1 month, less than 6 months), and schizophrenia (at least 6 months). The interviews were then presented and discussed with an expert psychiatrist for consensus diagnostic review. It was of the utmost importance that the diagnosis of non-affective early psychosis is made with high confidence.

Premorbid Adjustment

The Premorbid Adjustment Scale (PAS) measured social and academic functioning before the onset of psychosis across four developmental time periods (Cannon-Spoor et al., 1982). The scale covered childhood (ages 6-11), early adolescence (ages 12-15), late adolescence (ages 16-18) and adulthood (ages 19+) up to one year before the onset of psychosis and measures items related to social and academic functioning. Within each developmental stage, social (peer relationships, social withdrawal, socio-sexual behavior after childhood) and academic (grades, school behavior) items were measured. There are four items at childhood (peers, social withdrawal, grades, and school behavior), five for early and late adolescence (peers, social withdrawal, socio-sexual after childhood, grades, and school behavior), and three items for adulthood (peers, social withdrawal, and sociosexual). Therefore, no academic scores were available for the adulthood period. Each item was rated on a 0 to 6 scale, with

0 as healthy, normative development and 6 representing severe impairment. Scores were normalized to a 0 to 1 scale, providing scores as decimals, for ease of interpretation (Cannon-Spoor et al., 1982). PAS scores in this study were also reverse coded for ease of interpretation with dependent variables such that a 0 represented poor functioning and a score of 1 healthy, normative development.

The PAS was developed by Cannon-Spoor and colleagues to provide a retrospective, standardized interview and rating scale to measure this concept (Cannon-Spoor et al., 1982). The PAS is widely used in schizophrenia research and has good psychometric properties (interrater reliability: 0.74; validity evidence: discrimination of patients vs. healthy controls and known patient groups) (Cannon-Spoor et al., 1982). The interviewer established the onset of psychosis prior to the PAS interview (during the SCID, explained above) and included only those development stages 1 year before the onset. This is important to ensure we did not characterize a prodromal decline or pre-psychotic symptoms as part of the premorbid period. The interview was completed by a trained rater at the same session as the SCID. The PAS required roughly 30 minutes to administer and an additional 10 minutes for scoring. Independent variables of interest were created from the PAS data for social and academic domains separately as follows: intercept or initial starting point (childhood average of items within each domain) and slope of functioning across the developmental stages (beginning to end of premorbid phase to create a slope). This resulted in four primary independent variables of premorbid adjustment characterized as: social intercept, social slope, academic intercept, academic slope. The reliability of the PAS in this study was high for the full scale and domain sub-scales (Cronbach's alpha: Full scale: 0.816, Social subscale: 0.84, Academic subscale: 0.816).

Psychosocial Functioning

Two primary measures of post-onset psychosocial functioning were collected: the Personal and Social Performance Scale (PSP) and Quality of Life Scale (QLS) (Heinrichs et al., 1984; Morosini, Magliano, Brambilla, Ugolini, & Pioli, 2000). Both scales were completed in the same visit as the SCID.

Global Psychosocial Functioning. The PSP is a brief measure of psychosocial functioning that includes operationalized ratings of four items from 1 (absent) to 6 (very severe) for subscales of functioning including: social, occupational, independent living, and disturbing and aggressive behavior (Morosini et al., 2000). These scores across the four areas are utilized to provide a global rating of functioning on a 0 to 100 scale, with 0 being lowest, survival risk functioning, and 100 representing excellent functioning. The 0 to 100 scale is broken down into 10-point intervals that uses the combination of the 1 to 6 point ratings across the four subareas of functioning to operationalize the score. Any number can be given between 0 to 100, and the descriptions provided for each 10 point interval guide the interviewer in choosing a number in the 10 point interval. The scale has high inter-rater and intra-class reliability across disciplines (Weighted kappa on 10-point levels: 0.94; Kappa coefficient across discipline: 0.85; Intraclass coefficient: 0.98). The scale was rated after a short, open-ended interview about psychosocial functioning abilities and review of available medical records. In total the scale requires roughly 10 minutes to administer and score. The primary dependent variable of interest from the PSP was the score of 0 to 100 for the global functioning rating. The reliability of the PSP global score in this study was high (Cronbach's alpha: 0.824).

Social and Occupational Psychosocial Functioning. The QLS is a 21-item, semi-structured interview and rating scale that assesses social and occupational functioning, as well as intrapsychic foundations, for measurement of negative symptoms of psychosis (Heinrichs et al., 1984). The social and occupational sub-scales of this measurement tool were used as variables of interest in this study. The social subscale included 8 items for interpersonal relations and the occupational subscale included four items to measure instrumental role. One item from the occupational subscale was excluded as this item measured work role satisfaction rather than actual work performance. Each item was rated on a 0 to 6 scale, with a 0 representing severe impairment and 6 indicating normative functioning. An average score for each subscale was used as a measure of social and occupational functioning. The scale has

demonstrated high reliability as reported by a reliability study first completed by the three authors of the scale (Total: 0.94, Social: 0.94, Occupational: 0.97) and then by non-scale developers (Total: 0.88, Social: 0.87, Occupational: 0.94). Validity evidence was demonstrated in two ways: 1) sufficient fit for items to the proposed subscales and 2) good compatibility of the conceptual model demonstrated by a factor analysis. These statistics held true for both men and women patients when tested separately (Heinrichs et al., 1984). Dependent variables of interest from the QLS included the social and occupational subscales (average of items within each subscale), which were used as the outcome measures for social and occupational psychosocial functioning. Reliability for the full scale and subscales of the QLS for this study were high (Cronbach's alpha: Full scale: 0.903, Social subscale: 0.906, Occupational subscale: 0.874).

Power Analysis

A power analysis was completed using G*Power, version 3.1, for linear regression. For the power analysis the alpha value was set at 0.05, power was set at 0.95, four predictors were noted, and the medium f^2 effect size for R^2 was set at 0.19 from a 0.16 R^2 value. With these parameters, the total sample size required is 103. The current sample size of 104 is sufficiently powered for the planned analyses.

Data Analysis

The current study investigated social and academic premorbid adjustment patterns by psychosocial functioning (social, occupational, and global) at study entry. This study was conducted as an initial exploratory investigation as this is the first time detailed use of the PAS and subdomains of post-onset psychosocial functioning are included as primary areas of interest longitudinally in early psychosis. Descriptive statistics of means and standard deviations were completed for measurement scale data. Bivariate relationships were explored between all variables for the models. Linear regression was used with the four premorbid variables as predictors (social slope, social intercept, academic slope,

and academic intercept) and included social, occupational, or global psychosocial functioning measures as the dependent variable of interest. This resulted in three linear regression models, one for each dependent variable, that included all four premorbid variables as predictors, entered concurrently. Group differences by gender and race were explored with independent samples t-tests. Data were analyzed using SPSS, version 27 (IBM Corp., 2020).

Missing Data

Missing data were examined using the Missing Value Analysis in SPSS. No demographic variables were missing. The PAS had 2% of missing data. For the PSP, there was no missing data. For the QLS, there was 6.7% of missing data. These missing values were imputed using SPSS Expectation-Maximization method and the imputed data set used in the analysis.

Assumptions for Linear Regression

Assumptions for linear regression were tested thoroughly to ensure linearity of relationships between variables, normality of variables, absence of multicollinearity, independence of residuals, and homoscedasticity. Visual inspection of scatterplots of each IV and DV did not reveal any non-linear relationships supporting the use of linear regression. Normality of independent and dependent variables was assessed and met for premorbid slopes, global and social psychosocial functioning. However, academic and social intercepts and occupational functioning were not normally distributed. Therefore, bootstrapping was completed in addition to the standard linear regression to investigate differences in results. Bootstrapping results were reported to account for non-normality if results differed, but if the results were similar, standard results were reported. Multicollinearity was assessed by examining tolerance values with numbers less than 0.20 considered problematic. All tolerance values were above 0.20 so multicollinearity was not considered. Standardized residuals were assessed for independence and homoscedasticity. Durbin-Watson test for independence was completed with values outside of 1.5 and 2.5 considered problematic. All models had values in this range so independence of residuals was

met. Visual inspection of predicted values and standardized residuals were examined to ensure homoscedasticity was met for each analysis. Outliers were considered problematic if the residual was less than -3 or more than +3. Cook's D was also examined for meaningful outliers. Reliability of scales was assessed to ensure their sufficiency for the planned analyses.

Hypotheses

Hypothesized relationships between variables are summarized in Figure 3. I expected academic and social initial level and change throughout development to have significant main effects for global functioning at study entry. For the subscales of functioning, I anticipated that social premorbid trajectory and starting level would have significant main effects for social functioning at study entry, while academic premorbid change across the premorbid period and initial starting point would have significant effects for occupational functioning.

Results

Bootstrapping results were compared to traditional linear regression results and were consistent across the three analyses. Because no differences were noted, standard linear regression results are reported below.

Descriptive Statistics

Four premorbid variables were created and utilized for the analysis. The premorbid social slope range was -0.07 to 0.04 with an average value of -0.002 and standard deviation of 0.02. The premorbid academic slope included a range of -0.07 to 0.02 with an average value of -0.01 and standard deviation of 0.02. Negative slopes represent deterioration in functioning from childhood to the end of the premorbid period and positive slopes alternatively represent improvement from childhood level. The

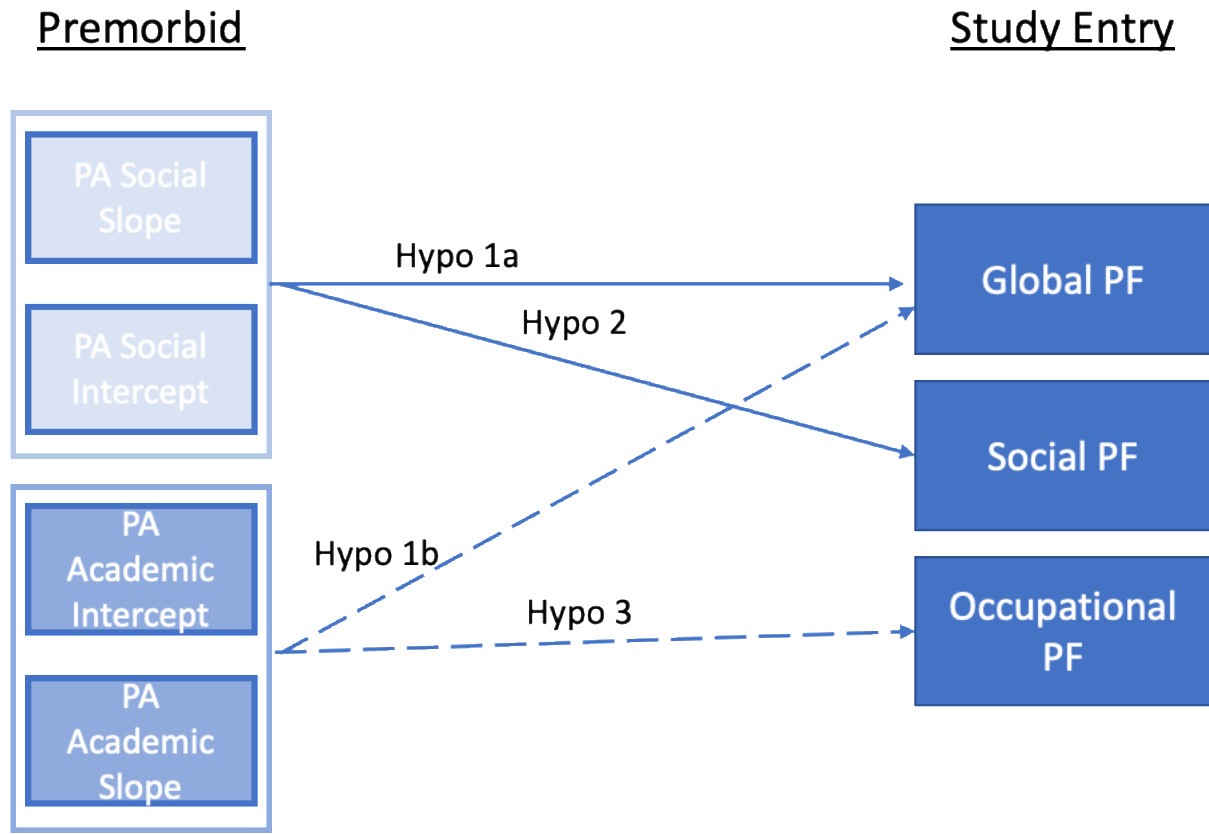


Figure 3. Hypothesized Relationships between Premorbid Adjustment (PA) and Psychosocial Functioning (PF) at Study Entry.

premorbid social intercept ranged from 0.42 to 1 with an average value of 0.78 and standard deviation of 0.19. The premorbid academic intercept ranged from 0.17 to 1 with an average value of 0.81 with a standard deviation of 0.19. An intercept value of 1 is good functioning, and lower values represent more difficulty. Therefore, these results indicate on average, patients tend to deteriorate over the premorbid phase (although this varies by individual), and is more steeply deteriorating for academic functioning than social. As a group, patients on average, have decent social and academic starting levels, with slightly lower social premorbid functioning.

Three dependent variables from two rating scales were used to measure post-onset global, social, and occupational psychosocial functioning. Global psychosocial functioning measured with the PSP has a possible range from 0 to 100, with higher numbers representing better functioning. This sample had a range of 18 to 90 [M: 50.66, SD: 17.9]. Social functioning, measured by the QLS, is an average score of 8 items from the QLS with a possible range of 0 to 6, with higher scores representing better functioning. Social functioning had a range of 0.25 to 6 [M: 3.35, SD: 1.45]. Occupational functioning was similarly measured by the QLS, including 3 items averaged to create this variable. The range of scores was 0 to 6 [M: 2.91, SD: 1.79]. There is a nice range of scores across the three scales, and on average, patients performed better socially than occupationally at study entry.

Bivariate Relationships

Table 2.1 shows bivariate results between independent and dependent variables for each model. Table 2.2 shows bivariate relationships between independent variables and Table 2.3 shows bivariate relationships between dependent variables. Baseline global functioning was significantly correlated with premorbid social slope and academic intercept. Social functioning at baseline was correlated with premorbid social slope, social intercept, and academic intercept. Occupational functioning at baseline was not significantly correlated with any premorbid variables. All three post-onset functioning measures were significantly correlated with each other. Premorbid social slope was

Table 2.1. Bivariate Relationships between Independent and Dependent Variables at Study Entry

	Global Functioning	Social Functioning	Occupational Functioning
PAS Social Slope	0.22*	.21*	0.1
PAS Social Intercept	0.06	.21*	0.03
PAS Academic Slope	0.12	0.08	0.03
PAS Academic Intercept	.22*	.21*	0.17 [^]

* $p < 0.05$, ** $p < 0.01$, [^] $p < 0.1$

Table 2.2. Bivariate Relationships between Independent Variables at Study Entry

	PAS Social Slope	PAS Social Intercept	PAS Academic Slope	PAS Academic Intercept
PAS Social Slope		-0.60**	0.26**	0.03
PAS Social Intercept			-0.05	0.13
PAS Academic Slope				-0.45**
PAS Academic Intercept				

* $p < 0.05$, ** $p < 0.01$, [^] $p < 0.1$

Table 2.3. Bivariate Relationships between Dependent Variables at Study Entry

	Global Functioning	Social Functioning	Occupational Functioning
Global Functioning		.67**	.67**
Social Functioning			.47**
Occupational Functioning			

* $p < 0.05$, ** $p < 0.01$, [^] $p < 0.1$

correlated with social intercept and academic slope. Academic slope was correlated with social slope and academic intercept. Social and academic intercepts were not correlated.

Post-Onset Global Functioning at Study Entry

The relationship between global psychosocial functioning at study entry and premorbid variables of social and academic slopes and intercepts was explored using linear regression analysis. All four premorbid variables were expected to be associated with post-illness global psychosocial functioning at study entry. The overall model was significant, $F(4, 103) = 4.74, p = 0.002$. As shown in Table 2.4, premorbid functioning variables of social and academic slope and intercept explained 16% of the variance in global functioning at study entry. Significant predictors of global psychosocial functioning included the slope of social premorbid functioning ($\beta = 0.296, sr_i^2 = 0.046$) and the intercept for academic functioning ($\beta = 0.267, sr_i^2 = 0.051$). Academic slope and social intercept were not significant variables in the model. These results partially support the hypothesis that premorbid variables were associated with global psychosocial functioning as the slope in premorbid social behavior and the initial academic premorbid level were significant predictors. The hypotheses were not fully supported as the expected relationships of the social intercept and change of academic performance over the premorbid period were not predictors of global functioning as expected.

Post-Onset Social Psychosocial Functioning at Study Entry

Study entry social functioning was also investigated in relationship to the premorbid variables. Initial premorbid social performance and change over the premorbid period in social performance (slope) were expected to be significantly associated with post-onset social functioning at baseline. Results from this model are shown in Table 2.5. The model was significant, $F(4, 103) = 8.05, p < 0.001$, with 24.5% of the variance in post-onset social functioning explained by the premorbid variables. As expected, both premorbid social intercept ($\beta = 0.497, sr_i^2 = 0.13$) and social slope ($\beta = 0.493, sr_i^2 = 0.139$)

Table 2.4. Regression Results for Global Functioning at Study Entry

	B	SE	Beta	<i>t</i>	<i>p</i>	CI Lower	CI Upper	sr_i^2
Constant	17.149	10.169		1.686	0.095	-3.029	37.326	
Social Slope	258.601	110.619	0.296	2.338	0.021	39.109	478.093	0.046
Academic Slope	172.755	108.974	0.178	1.585	0.116	-43.474	388.984	0.021
Social Intercept	20.272	11.55	0.213	1.755	0.082	-2.645	43.19	0.026
Academic Intercept	24.764	10.122	0.267	-3.382	0.016	4.679	44.849	0.051

Overall Model: $F(4, 103) = 4.74, p = 0.002$

$R^2 = 0.161; Adj R^2 = 0.127$

Table 2.5. Regression Results for Social Functioning at Study Entry

	B	SE	Beta	<i>t</i>	<i>p</i>	CI Lower	CI Upper	sr_i^2
Constant	-0.4	0.781		-0.513	0.609	-1.949	1.149	
Social Slope	35.073	8.492	0.497	4.13	<0.001	18.224	51.923	0.13
Academic Slope	3.142	8.366	0.04	0.376	0.708	-13.458	19.741	0.001
Social Intercept	3.789	0.887	0.493	4.273	<0.001	2.03	5.548	0.139
Academic Intercept	1.133	0.777	0.151	1.459	0.148	-0.408	2.675	0.016

Overall Model: $F(4, 103) = 8.052, p < 0.001$

$R^2 = 0.245; Adj R^2 = 0.215$

were significant predictors in the model. The two premorbid academic variables were not associated with social functioning. The hypothesized relationships in the model were supported as premorbid social variables predict post-onset social functioning at study entry. Premorbid academic functioning was not related to post-illness social functioning.

Post-Onset Occupational Psychosocial Functioning at Study Entry

Finally, the relationship of premorbid social and academic variables to occupational functioning at study entry was investigated. Academic premorbid variables of initial level and slope over time were expected to significantly predict occupational functioning. The model was not significant. Results are shown in Table 2.6. Contrary to the hypothesis, neither social nor academic premorbid variables were significant in the model to predict occupational functioning at study entry.

Exploratory Gender and Racial Group Differences

The unique contributions of race and gender on both premorbid and post-onset functioning were important to further investigate. The power analysis for this study indicated that exploring these interaction effects in our models were not suggested due to the sample size. As these questions were not the primary focus of the current investigation, the sample is described by gender and racial groups as a preliminary look at how these demographic variables may create differences in premorbid functioning and post-onset psychosocial functioning following an initial psychotic episode.

Gender Differences. Overall, the sample is predominantly male (77%), limiting explorations by gender due to a small female representation (19%). Despite that, there were differences in premorbid variables by gender for social slope (Males: $M: -0.004$, $SD: 0.02$; Females: $M: 0.006$, $SD: 0.02$; $t(102) = -2.14$, $p = 0.035$, Cohen's $d = -0.497$) and academic intercept (Males: $M: 0.79$, $SD: 0.20$; Females: $M: 0.87$, $SD: 0.14$; $t(102) = -2.14$, $p = 0.036$, Cohen's $d = -0.405$). These findings illustrate that the group of males have a declining pattern of social functioning over development whereas females have a more stable, even slightly increasing social slope. Females also had higher childhood academic performance

Table 2.6. Regression Results for Occupational Functioning at Study Entry

	B	SE	Beta	<i>t</i>	<i>p</i>	CI Lower	CI Upper	sr _i ²
Constant	0.981	1.082		0.907	0.367	-1.166	3.129	
Social Slope	9.288	11.773	0.106	0.789	0.432	-14.072	32.648	0.154
Academic Slope	9.674	11.598	0.099	0.834	0.406	-13.339	32.687	0.007
Social Intercept	0.661	1.229	0.07	0.538	0.592	-1.778	3.1	0.003
Academic Intercept	1.892	1.077	0.204	1.756	0.082	-0.245	4.03	0.03

Overall Model: $F(4, 103) = 1.313, p = 0.271$

$R^2 = 0.05; \text{Adj } R^2 = 0.012$

compared to their male counterparts. Gender differences were also found for outcome measures of post-onset global functioning (Males: $M: 48.59, SD: 17.88$; Females: $M: 57.58, SD: 16.47$; $t(102) = -2.20, p = 0.03$, Cohen's $d = -0.512$) and trend level significance for social functioning at study entry (Males: $M: 3.20, SD: 1.41$; Females: $M: 3.83, SD: 1.49$; $t(102) = -1.91, p = 0.059$, Cohen's $d = -0.444$). These post-onset outcomes show that females with early psychosis have better global and social functioning than males at study entry. Premorbid academic slope and social intercept and post-onset occupational functioning did not differ between men and women.

Racial Group Differences. The racial category breakdown of this sample included nearly two thirds white and about a third Black with little representation in other groups (2% Asian, 1% Other). To explore group differences by racial category, a new variable was created that collapsed all minority groups together in a non-white group for comparison to the white patients, resulting in 65% white and 35% non-white. No premorbid or post-onset functional outcome measures were different by racial group.

Discussion

Summary of Results

Premorbid adjustment patterns were explored for association with psychosocial functioning in early psychosis patients. This was a preliminary exploration of these relationships, as this is the first time detailed use of the PAS and subdomains of post-onset psychosocial functioning are included as primary areas of interest longitudinally in early psychosis. Separate trajectories of premorbid adjustment by domain of functioning, including social and academic functioning, were explored by calculating an intercept or initial starting level and slope or change throughout the premorbid period for each domain. Three models were created to investigate associations between the premorbid variables and psychosocial outcomes.

At study entry, premorbid adjustment was associated with both global and social psychosocial functioning. The global psychosocial functioning model included significant predictors of premorbid social change over time and academic starting level, with trend significance for social initial level. These results suggested that developmental information about how patients performed with peers and in school was related to subsequent psychosocial functioning following an initial episode of psychosis. Other studies reported similar relationships at study entry when assessing by premorbid domain score, particularly for premorbid social adjustment (Grau et al., 2016). Several studies demonstrated the relationship between type of PAS pattern, good versus poor, and consistently demonstrated relationships with global functioning (Addington et al., 2003; Haas & Sweeney, 1992). A similar study to the current investigation examined initial starting point and course of social and academic premorbid adjustment and explored the relationship to global functioning in early psychosis at baseline and also identified relationships, although these were small effects (T. K. Larsen et al., 2004). This study did not connect the course to the initial starting level, however, which was a limitation of this approach. In the current study, the initial level of academic performance in childhood and rate of social performance over time were robust predictors of psychosocial functioning. Social functioning following an initial episode of psychosis was predicted by both initial premorbid social level and trajectory of social performance throughout development. Another study also demonstrated this relationship with the PAS social domain significantly predicting social functioning at baseline (Jeppesen et al., 2008). Taken together, these results suggested the importance of developmental information to inform future psychosocial functioning after a diagnosis with a serious mental health disorder of psychosis. Initial academic level and social performance over time were significant predictors in these relationships, and will be important to follow-up with future studies.

Surprisingly, occupational performance at study entry was not significantly predicted by premorbid functioning. Other investigators have also failed to find significant relationships with

premorbid variables and post-onset occupational functioning at study entry (Grau et al., 2016; Jeppesen et al., 2008). Occupational functioning is often the most negatively impacted functional area by psychosis, as these educational and occupational roles and responsibilities are frequently disrupted beyond the short stay in a hospital with voluntary or mandated medical leave from places of employment and academic institutions. With that said, it was possible that measuring occupational functioning so early in the course of illness may artificially negatively bias this area of functioning more than the global or social functional outcomes due to extended enforced medical leave from some academic institutions or places of employment. These scores were much lower than social functioning at study entry which may support this idea.

Differences by gender and racial group were explored as a secondary analysis. Although the groups were not equally balanced on these demographic variables, differences by gender were found. Females had a positive social change over time and a higher starting level for academic performance compared to their male counterparts. Many studies have demonstrated women generally have better premorbid functioning than men (Abel, Drake, & Goldstein, 2010; Canuso & Pandina, 2007; Ochoa, Usall, Cobo, Labad, & Kulkarni, 2012). Additionally global and social psychosocial functioning at study entry were higher for females. A systematic review recently found that male sex was a predictor of relapse in schizophrenia (Bowtell, Ratheesh, McGorry, Killackey, & O'Donoghue, 2018; Ochoa et al., 2012). Other studies have consistently found that premorbid adjustment may mediate the differences in outcome between men and women with schizophrenia (Abel et al., 2010). These results suggest that female gender may be a protective factor in functional outcome and premorbid adjustment for early psychosis patients. Future studies should focus on confirming this pattern in a well powered, balanced sample to confirm this result. Additionally, future investigations regarding why female gender may be protective are also warranted. We did not find baseline differences by racial group as expected.

The current investigation improved on previous studies of the relationship between premorbid adjustment and post-onset psychosocial functioning in early psychosis in many ways. First, the use of the standardized rating scale the PAS has a demonstrated body of psychometric evidence to support its use and improve over other investigations of premorbid functioning that may include only informant reports, and medical record review, or investigate personality traits (MacBeth & Gumley, 2008). This study included many details of premorbid adjustment that are often lost through summary investigations that may include a single, overall average score of premorbid adjustment, or a single average for each domain or each developmental stage (MacBeth & Gumley, 2008). Additionally, we included all available development stages on an individual level, rather than cutting off the observation period in adolescence as many studies do. This ensures the entire premorbid period is represented for each individual rather than truncating the developmental range for the group as a whole. The current investigation includes only SCID verified non-affective psychotic disorders patients in the very early stages of illness. Many studies completed in the previous reviews include a mix of affective and non-affective psychotic patients resulting in a more mixed sample that is less focused on the early stages of schizophrenia. The outcome measures included in this study are a large improvement over the GAF or GAS of the previous review (MacBeth & Gumley, 2008). The GAF and GAS are problematic as the sole psychosocial outcome measure as these scales include symptom ratings with functional ratings, again creating a more mixed picture rather than purely focusing on psychosocial outcomes. We used objective, interview rated assessments that also improve the validity of experiences over self-report measures. Both scales for psychosocial outcome used in this investigation include detailed operationalizations of all items and scores with demonstrated improvements in reliability and validity evidence over the most commonly used scales of the GAF and GAS (Heinrichs et al., 1984; Morosini et al., 2000).

Limitations

This study was not completed without limitations. Investigations of premorbid adjustment are traditionally retrospective in nature, as the rating scales are completed after a person is diagnosed with a psychotic disorder. Prospective measurement of childhood and adolescence functioning would be an improvement to the retrospective rating scale; however, it would be very difficult to collect this prospective, longitudinal data. Future investigations of premorbid functioning may be improved if informant and school record data were collected and included in the scoring. This is more demanding for researchers and families of patients, but these efforts would improve upon the retrospective nature of the scale. This low incidence population was difficult to recruit and engage in research due to the illness itself which presents with disorganization, paranoia, and pronounced apathy at times. This increased the difficulty of recruiting this low incidence condition. Although we collected an acceptable sample size at study entry, the investigation in this study was limited by the sample size, especially for the exploration of more casual models or subgroups of patients by premorbid performance, outcomes, or different non-affective psychosis diagnosis groups. It was clear that gender differences, particularly in childhood and adolescence, may have had an impact on post-onset functioning following an initial psychotic episode. The current sample was underpowered to fully explore and understand these relationships. Finally, all subjects included in this study were service engaged, at least at the initial presentation. This could limit the generalizability of these findings by excluding patients who may not have access to care due to health insurance or other psychosocial difficulties like experiencing homelessness or imprisonment.

Future Directions

The current results inform many future potential explorations. Most importantly, this study was completed with patients at study entry, very early in their disease course. The findings here are an important first step, but future explorations that investigate how these patterns may uphold or change

over time to more distal follow-up along the course of a psychotic disorder are important next steps. The ultimate goal of this line of research is to best understand and predict who will have a good versus poor psychosocial outcome from psychosis. Following these patients over the course of their long-term illness will allow explorations of these associations for ultimate outcomes. Ideally, if we can best understand factors that lead to negative or positive outcomes, we could utilize this information to intervene through early interventions in psychosis. An understanding of premorbid strengths or challenges may best assist treatment providers in tailoring individual treatment options based on areas of developmental strength. Future longitudinal studies should also focus on differences in these premorbid patterns by non-affective psychotic disorder to best understand if these relationships are broadly affected by psychosis or more linked to negative or positive outcomes based on the ultimate diagnosis. Future explorations should also specifically design studies to more fully understand the role of gender in these functioning areas. The current study has a small representation of females, but in a larger study, more fully investigating the potential protective role of gender for females may also inform interventions and societal roles in recovery from a psychotic episode.

Conclusions

Premorbid adjustment patterns were associated with post onset social and global psychosocial functioning in non-affective early stage psychosis patients. Social performance over development and academic performance as a child predicted psychosocial functioning following an initial psychotic episode. Schizophrenia is a potentially severe and debilitating illness which majorly impacted psychosocial functioning even after psychotic symptoms are under control. Psychosocial interventions to support symptom remission and functional recovery in psychosis may be improved from including premorbid adjustment information to individually tailor treatments to patient areas of strength. The potential for these relationships to inform subsequent interventions will be bolstered by future investigations of these associations longitudinally.

CHAPTER III

**PREMORBID FUNCTIONING PATTERNS AND LONGITUDINAL POST-ILLNESS
PSYCHOSOCIAL FUNCTIONING IN THE EARLY STAGES OF PSYCHOSIS: A TWO-
YEAR FOLLOW-UP STUDY**

Abstract

In our previous study, premorbid functioning variables by domain and trajectory were significantly associated with post-onset global and social psychosocial functioning at study entry for non-affective early psychosis patients. The current investigation set out to demonstrate that these relationships would remain and strengthen with more distal follow-up periods, significantly improving the ability of premorbid variables in predicting subsequent outcomes in the early stages of illness. We expected to find similar relationships to the first study, with a specific hypothesis for initial and trajectory of academic premorbid performance and predicting two-year occupational functioning, which we did not find at study entry. In a prospective, longitudinal design, 78 early psychosis patients were included for the two-year follow-up visit. This study demonstrated an 85% retention rate. Premorbid variables of social and academic initial childhood level and rate of change over the pre-illness period were included as the predictors of interest. Post-onset two-year psychosocial functioning across social, occupational, and global functioning were the dependent variables of interest for each of the three linear regression models. Relationships to race and gender were also explored. Post-onset two-year global functioning was associated with premorbid academic initial level and change in performance across development. Post-onset two-year social functioning was significantly predicted by social trajectory and starting point and the initial academic level of premorbid functioning. Post-onset two-year follow-up occupational functioning was associated with both academic premorbid variables. The race differences were explored in this sample of 78, and those in non-white racial group had lower social functioning at baseline and were more likely to be lost to follow-up for the longitudinal visit. This study confirms the relationships seen at study entry for pre-illness functioning and post-onset psychosocial functioning remain at two-year follow-up, with the addition of occupational functioning after the initial presentation. These relationships illustrate the value of assessing and considering premorbid functioning patterns when investigating or treating psychosocial functioning in the early stages of psychosis. Those

who belonged to a non-white racial group presented with lower social functioning and were more likely to drop out of the study. These findings warrant further study in more directed investigations.

Introduction

Premorbid functioning is a robust prognostic indicator for a variety of clinical outcomes in schizophrenia and is associated with post-onset psychosocial functioning at study entry in early psychosis (MacBeth & Gumley, 2008; Malla & Payne, 2005; Van Mastrigt & Addington, 2002). Psychosocial functioning is often severely impaired in chronic schizophrenia patients, but many early psychosis patients remit and recover after an initial episode of psychosis with nearly one third never having a psychotic episode relapse in the future (Fusar-Poli et al., 2016). Following patients over time, including those who do and do not continue to struggle with psychotic symptoms, is imperative for investigations of outcome in schizophrenia, particularly to best inform future interventions to support recovery. Longitudinal efforts with early psychosis patients are necessary to understand how these patterns develop or change over illness course and relate this to predictors of individual strengths for recovery. Relationships between premorbid adjustment and future post-onset psychosocial functioning may be an important strategy for understanding patterns of functional outcome in this highly heterogenous condition.

The association between premorbid functioning and post-onset psychosocial functioning has been demonstrated longitudinally in early psychosis samples. Global psychosocial functioning was associated with premorbid social functioning at 1 year, 3 year, and 5 year follow-up (Ayesa-Arriola et al., 2013; R. M.G. Norman et al., 2012; Simonsen et al., 2007). These results illustrate the important role developmental social functioning prior to psychotic illness has in predicting future post-onset psychosocial functioning. However, these results do not allow us to examine when in development this holds true. Premorbid domain of functioning also have demonstrated associations with sub-domains of social or occupational post-onset functioning. Social premorbid performance was related to post-onset social functioning at 1 year follow-up (Jeppesen et al., 2008). Post-onset occupational functioning was associated with premorbid academic performance at 1 year, 2 year, and 5 year follow-up in early psychosis (Albert et al., 2011; Jeppesen et al., 2008; Ross M G Norman et al., 2015). Additionally,

premorbid social functioning was associated with 5 year follow-up occupational functioning in one study (Albert et al., 2011). Although many studies have preferred a premorbid domain approach over developmental investigations, premorbid adjustment during late adolescence was associated with 1 year global and social post-onset functioning in several studies pointing to the importance investigations including the premorbid trajectory by domain (Canal-Rivero et al., 2019; Tor K. Larsen, Moe, Vibe-Hansen, & Johannessen, 2000; Üçok, Polat, Çakir, & Genç, 2006).

The current study builds on this small body of research to comprehensively investigate longitudinal relationships between premorbid domain by trajectory and relationships to social, occupational, and global post-onset functioning at two-year follow-up. We used all available premorbid data for each individual to map out trajectories separately for social and academic functioning. This sample was purely non-affective psychosis, the precursor to schizophrenia, with verified two-year diagnoses which was an improvement over many studies with a single diagnostic interview. Similar to study entry predictions, we expected that premorbid social initial level and trajectory over time will be associated with post-onset social functioning, and academic starting level and course over time will be predictive of occupational functioning. We similarly anticipated that all premorbid variables will be associated with global functioning at two-year follow-up.

Methods

Research Design

The current study was a prospective, longitudinal design, which followed early psychosis patients two years after study entry to assess distal outcomes following an initial psychotic episode. In the previous study, discussed in Chapter II, patients were able to enter the study up to two years after the onset of psychosis. Therefore, our sample included follow-up periods within individual courses of illness from two to four years post-onset. The two year time frame was chosen to align with the critical period hypothesis of the first two to five years as the period of anticipated decline. This early psychosis

longitudinal study was completed from 2013 until the March 2020 when the current pandemic began, making it difficult to continue in-person research. Of the original 104 subjects included at baseline, 26 were not able to complete the two year visit due to the pandemic and travel restrictions. Of the 78 subjects who were eligible to complete the two year visit prior to the pandemic, 11 were lost to follow-up. This retention rate of 86% is high, particularly for a severe mental health disorder like psychosis.

Subjects

Data Collection

All subjects who completed the two-year follow-up, were invited back to repeat all assessments completed at study entry with the exception of the PAS, which is a retrospective scale for the premorbid period, and therefore would not change over time like the other assessments. A full, comprehensive SCID interview was repeated at follow-up with a focus on psychosis symptom course to provide psychotic disorder diagnoses. All medical records from Vanderbilt and outside hospitals, clinics, and rehabilitation treatment were obtained, with permission from the subjects. This information was highly valuable to increase confidence in the diagnostic assessment. Diagnostic consensus review meetings were completed for two-year diagnoses. Again, only patients with a non-affective psychotic disorder were included in this study. The three post-onset psychosocial functioning interviewer rated scales were completed to measure functioning two years after original study entry including the PSP for global functioning and the QLS for social and occupational psychosocial functioning.

Reliability for study instruments was assessed using Cronbach's alpha, and, similar to study entry, high reliability was found for all rating scales. The PAS had an alpha of 0.80 (Social Subscale: 0.82, Academic Subscale: 0.81). Reliability for dependent variables at two-year was good (PSP: 0.832; QLS: 0.894). The QLS sub-scales also had high reliability at two-year (Social: 0.90; Occupational: 0.83).

Sample Characteristics

This longitudinal study included 78 subjects with verified non-affective psychotic disorders. The diagnostic breakdown at the two-year visit included: 23% Schizophreniform Disorder, 13% Schizoaffective Disorder, 50% Schizophrenia, and 14% lost to follow up. For comparison and insight into the disease progression, the diagnostic make-up at study entry included: 65% Schizophreniform Disorder, 9% Schizoaffective Disorder, and 26% Schizophrenia. Many patients progressed from short term (each episode less than 6 months) psychosis diagnosed with Schizophreniform Disorder at baseline to Schizophrenia or Schizoaffective Disorder which includes at least one psychotic episode of 6 months in duration. The follow-up sample included 79% male and 21% female and 73% White, 24% Black, and 3% Asian. The average age at study entry for the current sample was 21.37 (SD = 3.75) with a range of 16 and 39.

Power Analysis

A power analysis was completed using G*Power, version 3.1, for linear regression, for the study entry analysis. To briefly provide a reminder of that analysis: Alpha value was set at 0.05, power set at 0.95, four predictors were included, and medium f^2 effect size for R^2 set at 0.19 from a 0.16 R^2 value. With these parameters, the total sample size required is 103. The current sample size of 78 is slightly underpowered according to these results.

Data Analysis

The current study investigated relationships of premorbid social and academic patterns with post-onset psychosocial functioning (social, occupational, and global) two years after study entry in order to assess premorbid variables relationship to long-term outcomes in psychosis. Given power limitations, this study was conducted as an initial, exploratory investigation as these complex and focused relationships have not been investigated thoroughly with sub-domains of psychosocial functioning over the early stages of psychosis. Differences between those who did and did not complete

the follow-up visit (67 completers versus 11 non-completers) were compared on demographic, predictor, and outcome variables using independent samples t-tests and Chi-square tests where appropriate. The two-year follow-up sample was described as a whole for predictor and outcome variables, and these outcome variables were compared to study entry results using paired samples t-tests. Bivariate relationships between predictor and outcome variables were explored and described. Linear regression was used with the four premorbid variables as predictors (social slope, social intercept, academic slope, and academic intercept) and included social, occupational, or global psychosocial functioning measures as the dependent variable of interest. This resulted in three linear regression models, one for each dependent variable. Group differences by gender and racial group were explored with independent samples t-tests. Demographic variables were not included in the model due to power limitations. Data were analyzed using SPSS, version 27 (IBM Corp., 2020).

Missing Data

Missing data were examined and approached using the Missing Value Analysis in SPSS. No demographic variables were missing. The PAS had 1% of missing data. The PSP and QLS had 14.1% missing data. These missing values were imputed using SPSS Expectation-Maximization method and used in the analysis.

Assumptions for Linear Regression

Linear regression assumptions were tested to ensure appropriateness of the chosen analytic method. Linearity of the data was ensured by visual inspection of scatterplots for each independent variable with each dependent variable. No non-linear relationships were identified through this method. Normality of all variables was inspected through histogram plots and normality was confirmed for two-year global psychosocial functioning and premorbid slopes. However, academic and social intercepts and social and occupational functioning variables were not normally distributed. Bootstrapping for confidence intervals was completed to ensure results were not biased by the non-normal variables. If

bootstrapping and standard regression results were similar, standard regression results were reported rather than bootstrapping results. Multicollinearity was assessed by examining tolerance values with numbers less than 0.20 considered problematic. All tolerance values were above 0.20 so multicollinearity was not considered problematic. Independence of residuals was assessed by the Durbin-Watson test for independence. All values were within the suggested range of 1.5 and 2.5 suggesting independence of residuals was met. Visual inspection of predicted values and standardized residuals were examined to ensure homoscedasticity was met for each analysis. Outliers were considered problematic if the residual was less than -3 or more than +3. Cook's D was also examined for meaningful outliers. Only one analysis (two-year occupational functioning as DV) had two meaningful outliers in this range, and these were removed from the analysis. The other analyses were free from problematic outliers. Reliability of scales was assessed to ensure this is sufficient for the planned analyses.

Hypotheses

Figure 4 shows the proposed relationships between variables for the three analyses at two-year follow-up. It was expected that academic and social slopes and intercepts would be associated with two-year global functioning. It was hypothesized that for the subscales of functioning, social premorbid slopes and intercepts would be significant effects on two-year follow-up social functioning, while academic premorbid slope and intercepts would be associated with two-year follow-up occupational functioning.

Results

Due to non-normality in some variables, bootstrapping results were completed and compared to the standard linear regression results. There were no meaningful differences in these two results, therefore, the standard results will be reported rather than the bootstrapped results.

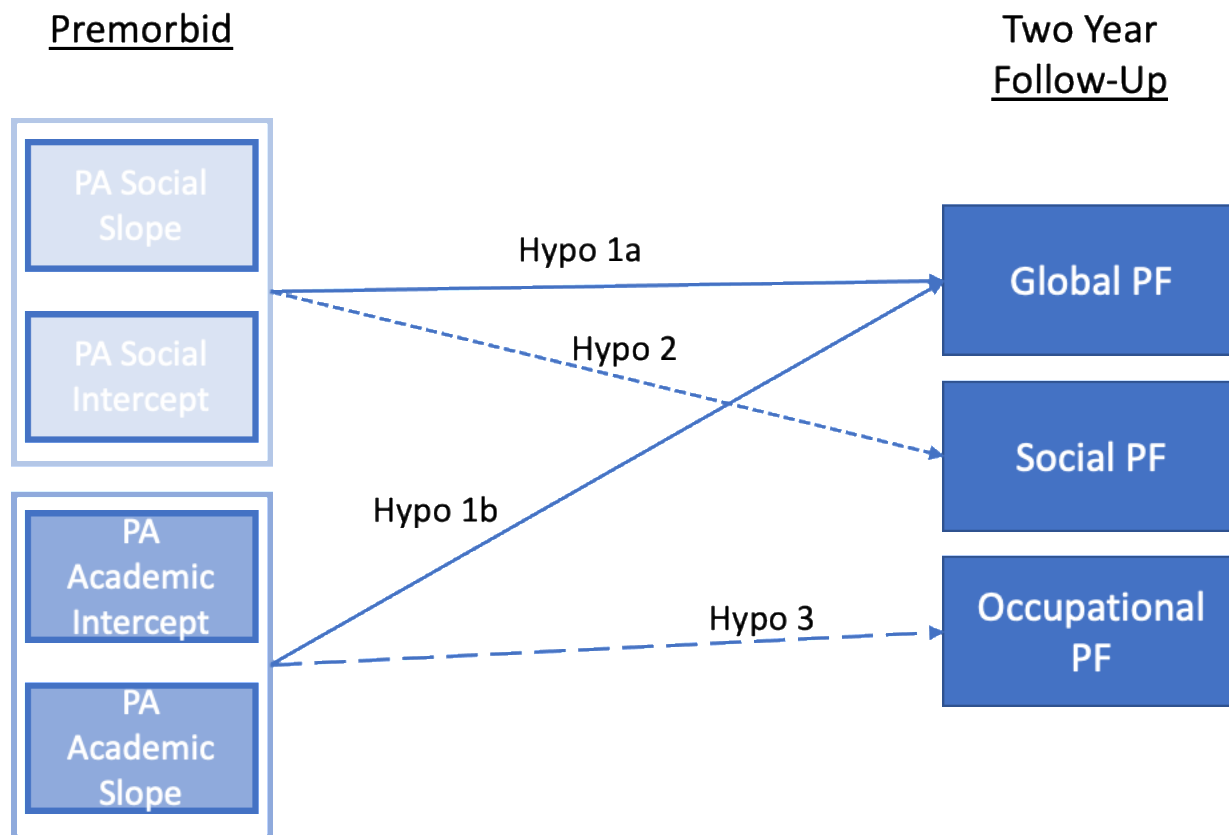


Figure 4 Hypothesized Relationships between Premorbid Adjustment (PA) and Psychosocial Functioning (PF) at Two-Year Follow-Up.

Descriptive Statistics

For the 78 participants eligible for the two-year follow-up visit, 67 completed the longitudinal visit and 11 were lost to follow-up. Although this is a high retention rate for a longitudinal study in psychosis, it is important to understand any differences that may bias or question the generalizability of the results. Demographically, patients in the two groups were similar on age and gender. The group of non-completers had higher representation of non-white participants than completers (Non-completers 45% White, 54% Non-White; Completers: 77% White, 22% Non-White; $\chi^2(1, N = 78) = 4.966, p = 0.026$). The two groups did not differ on premorbid variables, but psychosocial functioning at baseline for global (Completers: $M: 51.34, SD: 18.90$; Non-Completers: $M: 39.00, SD: 15.11$; $t(76) = 2.057, p = 0.043$, Cohen's $d = 0.669$) and social (Completers: $M: 3.42, SD: 1.49$; Non-Completers: $M: 2.18, SD: 1.28$; $t(76) = 2.612, p = 0.011$, Cohen's $d = 0.85$) functioning was significantly different between groups. These results suggest that those who did not return for their follow-up visit are more likely to be a non-white and have more trouble functioning at study entry, especially social functioning.

Summary statistics for the four premorbid independent variables was similar to the study entry values. The premorbid social slope range was -0.07 to 0.04 ($M: -0.003; SD: 0.02$). The premorbid academic slope included a range of -0.07 to 0.02 ($M: -0.01; SD: 0.02$). The premorbid social intercept ranged from 0.42 to 1 ($M: 0.78; SD: 0.18$). The premorbid academic intercept ranged from 0.17 to 1 ($M: 0.80; SD: 0.20$). These patterns are quite similar to the study entry results as there is great overlap in these samples. Overall, as a group, the patients tended to decline across the premorbid period, with more decline observed in academic functioning compared to social. On average the group demonstrated good social and academic starting levels (intercepts), with a bit higher levels of academic versus social premorbid functioning.

Three dependent variables from two rating scales were used to measure post-onset global, social, and occupational psychosocial functioning. This sample had a range of 22 to 95 ($M: 60.04; SD:$

18.10) for global functioning. Social functioning had a range of 0.75 to 6 ($M: 4.05; SD: 1.39$). Occupational functioning had a range of scores of 0 to 6 ($M: 4.45; SD: 1.55$). Overall, these means are significantly higher at follow-up across the three scales than at study entry illustrating that patients on average were doing better at the longitudinal follow-up visit than at study entry. Global psychosocial functioning improved by roughly 10 points from study entry to two-year follow-up (Study Entry: $M: 49.86, SD: 18.96$; Follow-Up: $M: 61.39, SD: 17.24$; $t(75) = -5.48, p < 0.001$, Cohen's $d = -0.628$). Social functioning was significantly improved at two-year follow-up also (Study Entry: $M: 3.30, SD: 1.50$; Follow-Up: $M: 4.11, SD: 1.35$; $t(75) = -5.178, p < 0.001$, Cohen's $d = -0.594$). Occupational functioning improved more sharply than social functioning at two-year and was higher on average than social functioning at follow-up (Study Entry: $M: 2.86, SD: 1.76$ Follow-Up: $M: 4.57, SD: 1.39$; $t(75) = -8.595, p < 0.001$, Cohen's $d = -0.986$).

Bivariate Relationships

Table 3.1 shows bivariate results between independent and dependent variables for the three models. Bivariate results between independent variables in shown in Table 3.2 and between dependent variables in Table 3.3. Two year global functioning was significantly correlated with premorbid academic intercept. Social functioning at follow-up was correlated with premorbid academic intercept. Two-year occupational functioning was significantly correlated with academic slope. All three post-onset two-year functioning measures were significantly correlated with each other. Premorbid social slope was correlated with social intercept and academic slope. Academic slope was correlated with social slope and academic intercept. Social and academic intercepts were not correlated.

Post-Onset Global Functioning at Two-Year Follow-Up

Linear regression was used to investigate the relationship between premorbid social and academic variables to post illness two-year follow-up global psychosocial functioning. Both initial and

Table 3.1. Bivariate Relationships between Independent and Dependent Variables at Two-Year Follow-Up.

	Global Functioning	Social Functioning	Occupational Functioning
PAS Social Slope	0.12	0.21 [^]	0.2 [^]
PAS Social Intercept	0.07	0.15	0.01
PAS Academic Slope	0.05	0.03	0.25 [*]
PAS Academic Intercept	0.41 ^{**}	0.34 ^{**}	0.22 [^]

* $p < 0.05$, ** $p < 0.01$, [^] $p < 0.1$

Table 3.2. Bivariate Relationships between Independent Variables at Two-Year Follow-Up.

	PAS Social Slope	PAS Social Intercept	PAS Academic Slope	PAS Academic Intercept
PAS Social Slope		-0.63 ^{**}	.28 [*]	0.05
PAS Social Intercept			-0.05	0.07
PAS Academic Slope				-0.49 ^{**}
PAS Academic Intercept				

* $p < 0.05$, ** $p < 0.01$, [^] $p < 0.1$

Table 3.3. Bivariate Relationships between Dependent Variables

	Global Functioning	Social Functioning	Occupational Functioning
Global Functioning		0.72 ^{**}	0.70 ^{**}
Social Functioning			0.38 ^{**}
Occupational Functioning			

* $p < 0.05$, ** $p < 0.01$, [^] $p < 0.1$

trajectory of social and academic premorbid adjustment variables were anticipated to be significantly associated with post-onset global psychosocial functioning at two-year follow-up. The model was significant, $F(4, 77) = 4.526, p = 0.003$, with 19.9% of the variance in global psychosocial functioning explained by the premorbid variables in the model. Table 3.4 shows the regression results. At two year follow-up, global functioning was predicted by the academic intercept ($\beta = 0.49, sr_i^2 = 0.16$) and academic slope ($\beta = 0.284, sr_i^2 = 0.049$), but the social premorbid variables were not significant. The hypothesized relationships were partially supported through the academic premorbid variables, but interestingly, social variables were not significant.

Post-Onset Social Psychosocial Functioning at Two-Year Follow-Up

Linear regression was used to investigate the relationship with premorbid social and academic variables with post-illness two-year follow-up social functioning. As with the study entry data, both social intercept and slope were hypothesized to be related to two-year social functioning. The model was significant, $F(4, 77) = 5.258, p < 0.001$, with 22.4% of the variance in two-year social functioning explained by the premorbid variables in the model. Results of the analysis are presented in Table 3.5. As expected, both premorbid social variables of slope ($\beta = 0.398, sr_i^2 = 0.075$) and intercept ($\beta = 0.344, sr_i^2 = 0.064$) were significant in the model. In addition, premorbid academic initial level ($\beta = 0.302, sr_i^2 = 0.061$) was also significant, but academic slope was not. Results are summarized in Table 3.5.

Post-Onset Occupational Psychosocial Functioning at Two-Year Follow-Up

The final linear regression model investigated premorbid variables' relationship to post-illness two-year follow-up occupational functioning. The hypothesis was that premorbid academic slope and intercept were related to two-year occupational functioning. The model was significant, $F(4, 75) = 5.086, p = 0.001$, with 22.3% of the variance in two-year occupational functioning explained by the premorbid variables in the model. These results are summarized in Table 3.6. As expected, both

Table 3.4. Global Functioning Regression Results at Two-Year Follow-Up

	B	SE	Beta	<i>t</i>	<i>p</i>	CI Lower	CI Upper	sr_i^2
Constant	25.183	12.028		2.094	0.04	1.211	49.155	
Social Slope	42.658	125.128	0.052	0.341	0.734	-206.721	292.037	0.001
Academic Slope	250.617	118.548	0.284	2.114	0.038	14.352	486.883	0.049
Social Intercept	3.26	14.09	0.033	0.231	0.818	-24.822	31.342	0.001
Academic Intercept	43.865	11.488	0.49	3.818	< 0.001	20.969	66.761	0.16

Overall Model: $F(4, 77) = 4.526$, $p = 0.003$
 $R^2 = 0.199$; $Adj R^2 = 0.155$

Table 3.5. Social Functioning Regression Results at Two-Year Follow-Up

	B	SE	Beta	<i>t</i>	<i>p</i>	CI Lower	CI Upper	sr_i^2
Constant	0.515	0.906		0.568	0.572	-1.291	2.32	
Social Slope	25.081	9.426	0.398	2.661	0.01	6.295	43.866	0.075
Academic Slope	6.874	8.93	0.102	0.77	0.44	-10.923	24.672	0.006
Social Intercept	2.602	1.061	0.344	2.451	0.017	0.487	4.717	0.064
Academic Intercept	2.068	0.865	0.302	2.39	0.019	0.344	3.793	0.061

Overall Model: $F(4, 77) = 5.258$, $p < 0.001$
 $R^2 = 0.224$; $Adj R^2 = 0.181$

Table 3.6. Occupational Functioning Regression Results at Two-Year Follow-Up

	B	SE	Beta	<i>t</i>	<i>p</i>	CI Lower	CI Upper	sr_i^2
Constant	2.176	0.915		2.377	0.02	0.351	4.002	
Social Slope	6.232	9.47	0.1	0.658	0.513	-12.65	25.114	0.005
Academic Slope	29.176	9.033	0.434	3.23	0.002	11.165	47.188	0.114
Social Intercept	0.505	1.07	0.067	0.472	0.638	-1.628	2.638	0.002
Academic Intercept	2.874	0.874	0.422	3.29	0.002	1.132	4.616	0.118

Overall Model: $F(4, 75) = 5.086$, $p = 0.001$
 $R^2 = 0.223$; $Adj R^2 = 0.179$

academic slope ($\beta = 0.344$, $sr_i^2 = 0.064$) and intercept ($\beta = 0.344$, $sr_i^2 = 0.064$) were significant predictors in the model but social premorbid variables were not. The hypothesized relationships of this model were supported by the results.

Exploratory Gender and Racial Group Differences

As with study entry data, the role of gender and racial group were explored for group differences. These variables were not added to the above models, due to limited power, but were explored for differences as secondary questions for the overall analysis.

Gender Differences. The longitudinal sample was similarly unbalanced by gender with 80% males and 20% females. No premorbid or post-onset follow-up outcomes were significantly different by gender, but two variables were noted to have trend level significance. Premorbid social slope approached significance with females having a positive, improving slope while males have a negative, declining social slope over development (Males: $M: -0.005$, $SD: 0.02$; Females: $M: 0.006$, $SD: 0.02$; $t(74) = -1.71$, $p = 0.091$, Cohen's $d = -0.493$). Baseline global functioning was trending towards significance in this longitudinal follow-up sample as found in the larger study entry sample (Males: $M: 47.79$, $SD: 18.98$; Females: $M: 58.27$, $SD: 16.96$; $t(74) = -1.953$, $p = 0.055$, Cohen's $d = -0.563$). No other premorbid variable or two-year social or occupational outcome were different by gender. These results suggest the protective factor of gender at study entry may not carry forward to more distal outcomes in psychosis, although this interpretation should be made cautiously due to the small and unbalanced sample.

Racial Group Differences. The racial category breakdown of this sample was predominantly white (72%) and a quarter Black (25%) with little representation in other groups (2.6% Asian). To explore group differences by racial category, a new variable was created that collapsed all minority groups together in a non-white group for comparison to the white patients, resulting in 72% white and 27.6% non-white. No premorbid variables differed by race, but some differences were identified by racial group in two-year post-onset functional outcome measures. Two-year social functioning was different

by racial category (White: $M: 4.33$, $SD: 1.22$; Non-White: $M: 3.52$, $SD: 1.51$; $t(74) = 2.401$, $p = 0.019$, Cohen's $d = 0.616$). Global functioning at two-year follow-up had trend level difference between groups (White: $M: 63.76$, $SD: 17.08$; Non-White: $M: 55.19$, $SD: 16.44$; $t(74) = 1.976$, $p = 0.052$, Cohen's $d = -0.507$). These results suggest that being a member of a non-white racial group may lead to worse social and global psychosocial functioning.

Discussion

Summary of Results

In this study, premorbid adjustment was explored for associations with distal, longitudinal psychosocial outcomes in non-affective early psychosis patients as a follow-up to the study entry results presented previously. Unlike at study entry, all three models were significant illustrating the strength of the relationships between premorbid adjustment and post-onset psychosocial functioning. Global psychosocial functioning was significantly predicted by premorbid academic performance, both the initial childhood level (intercept) and change over premorbid period (slope). Interestingly, social premorbid initial level and change over development were not significant predictors of two-year global functioning although social premorbid functioning has often been identified as a significant predictor of global functioning (Ayesa-Arriola et al., 2013; R. M.G. Norman et al., 2012; Simonsen et al., 2007). Performance in school as a child and adolescent, both from the initial starting performance and the change of this performance across the developmental period, were related to functional ability two-years after an initial psychotic episode.

In the present study, post-onset social functioning at two-year follow-up was associated with premorbid social initial level and developmental trajectory and initial academic performance. This may mean that developmental social performance is tied to social ability later in life and childhood academic performance predicts social functioning. One other identified study found a similar relationship between average PAS social performance with longitudinal social functioning at 1 year follow-up (Jeppesen et al.,

2008). It is somewhat surprising to find the relationship of initial premorbid academic performance as a significant predictor of social functioning, but this may point to the importance of cognitive development to future social functioning. No other study assessing these relationships found support for academic premorbid functioning as a predictor of post-onset social functioning, so this finding deserves future attention to see if it is replicated. Unlike the study entry findings, two year occupational functioning was significantly predicted by premorbid academic initial childhood level and rate of change over the pre-illness period, illustrating the predictive power of developmental performance to future occupational functioning two years after an initial psychotic episode. Social premorbid variables were not significant in the occupational functioning model. These results signify the importance of premorbid academic performance to future educational or occupational functioning later in life. Many other longitudinal studies investigating these relationships have reported similar findings between premorbid academic performance and post-onset occupational functioning at 1 year, 2 year, and 5 year follow-up periods (Albert et al., 2011; Jeppesen et al., 2008; Ross M G Norman et al., 2015). Taken together, the associations between these separate, specific premorbid variables and later psychosocial functioning were strong and provide specific information based on domain of functioning. This demonstrates the importance and necessity of breaking the premorbid data down into its sub-units for a comprehensive exploration of predicting social, occupational, and overall psychosocial functioning in psychotic disorders.

This sample was predominantly male (80%) and white (72%). Group differences based on gender and race were explored and displayed different results than the study entry data. No gender differences were found in this smaller, longitudinal sample. However, racial group demonstrated worse social functioning at two-year follow-up for the non-white group. With the caveat that this group was quite small, these results suggest that being a member of a non-white racial group may lead to worse longitudinal social outcomes. There are few studies specifically investigating the impact of race on

psychosocial functioning in schizophrenia (Kidd, 2013). However, a landmark meta-analysis about migration as a social risk factor for schizophrenia found that all migrants in various countries are at an increased risk of developing schizophrenia, both first and second generation migrants (Selten, Cantor-Graae, & Kahn, 2007). This meta-analysis also found that this risk was even higher for migrants coming from countries with predominantly Black populations. The authors hypothesize that racial discrimination along with social challenges such as poverty, unemployment, and family dysfunction may cause this notable disparity (Selten et al., 2007). Despite clear evidence in the literature for social functioning differences in white and non-white patients, it has been well documented that race differentially impacts who will receive a diagnosis of schizophrenia versus other related disorders (Eack, Bahorik, Newhill, Neighbors, & Davis, 2012; Gara, Minsky, Silverstein, Miskimen, & Strakowski, 2019). The current investigation was not designed to investigate gender and racial differences as a primary outcome, but this finding, and the study entry findings of females with better outcomes than males, suggest further explorations with these demographic and societal factors as the primary objective are warranted.

Limitations

This study presented two-year longitudinal results for psychosocial functioning in early psychosis. Although the study was completed with a high retention rate (85%), particularly for a sample with serious and persistent mental health concerns, the sample was a bit underpowered. Because this sample was analyzed as an initial exploration of these complex patterns, the analysis was conducted with this caveat in mind. Although only 11 participants did not complete the two-year follow-up, these participants were more likely to be non-white and had lower global and social functioning at study entry. This represents potential attrition bias as those with lower functioning were less likely to follow up. The sample here was recruited from an academic medical center and all subjects were recruited in a service engaged environment. Not all participants remained service engaged along the longitudinal follow-up period, but the initial recruitment occurs in this setting. This is a limitation as we may be

missing potential early psychosis patients who do not engage with psychiatric services, such as individuals experiencing homelessness or those without health insurance. Future studies that include a larger, more generalizable sample outside of traditional service settings would be an important future step to more fully represent the variability of early psychosis patients. Future investigations should focus on extending this longitudinal sample for more power and to testing if the identified relationships hold up in a larger sample. Despite this, we identified many important relationships that may inform future studies and interventions from a strengths based perspective. The pandemic brought a halt to many in-person research activities which limited completion of longitudinal follow-up participants for this study. The vast majority of longitudinal studies have some data loss from patient drop out, and this is especially problematic for this population. Because of the power issue and being the first study of its kind, this was a first pass exploratory study to inform future studies of causal relationships for these models. Finally, the role of medication is not fully understood in these results and deserve focus in future investigations. These results are limited in interpretation because of this, but many important relationships have been identified and will be followed up in future investigations.

Future Directions

Results from this study point to many important future questions related to this work. We found significant relationships at two-year follow-up in early psychosis patients with premorbid adjustment patterns. It would be an important next step to continue to follow this sample in more distal follow-up periods to explore if these associations hold up to long term follow-up for more chronically ill patients. Despite the limitations of a small and unbalanced sample, this identified difference in two-year social functioning by racial group, may point to important considerations for future psychosocial interventions with sensitivity and individualized treatments by race. Future investigations that are well powered and more diverse are an important next step to extend these findings. Because this sample was collected as part of a neuroimaging study, a future investigation that explores relationships to brain structure and

cognition would be an important next step, as no brain volume studies have been conducted with these relationships to premorbid adjustment performance. Etiological theories of schizophrenia include a neurodevelopmental model, lower brain volume and cognitive difficulties from birth, versus a neurodegenerative model, brain changes and cognitive difficulties mostly emerge as a result of the illness. Using PAS patterns to relate to these two models could be informative if linked to the brain patterns and structural differences. Ultimately, future studies should also include individualized psychosocial interventions focusing on previous developmental strengths or challenges to support recovery from psychosis.

Conclusions

Premorbid adjustment patterns were significantly associated with two-year follow-up psychosocial functioning in early psychosis patients. The initial starting level of academic performance in childhood was predictive of all three functional outcomes while social change over time and initial social performance level were predictive of social functioning. Academic developmental change was also predictive of occupational functioning. Exploratory secondary analyses revealed differences in social functioning at two-year follow-up by racial group with the non-white group demonstrating worse performance. These results reveal the importance of utilizing premorbid domains and developmental trajectory to inform future psychosocial functioning. These results lend themselves to future development of individually tailored psychosocial rehabilitation interventions for those struggling with psychotic disorders.

CONCLUSIONS & RECOMMENDATIONS

Schizophrenia is a mental health disorder that affects roughly 1% of the population yet ranks 11th of health conditions in economic burden caused by disabilities (H. Y. Chong et al., 2016; Eaton et al., 2008; Vos et al., 2015). This significant psychosocial disability caused by psychosis persists despite resolution of psychotic symptoms, and these impairments are often long-term, even lifelong in many patients (Ayano et al., 2019; Eaton et al., 2008). Regaining the ability to successfully pursue educational and occupational opportunities, interact with people in society, and generally manage day to day activities is a priority for patients, families, providers, and society at large in patients with psychosis. The research reported here set out to establish relationships between psychosocial functioning and subcomponents of premorbid adjustment (social and academic initial childhood level and rate of change over the pre-illness period), a well-known prognostic indicator for schizophrenia. First, a systematic review was completed to provide an update to a previous review completed in 2007 that assessed these relationships and to improve and expand on the method and included variables. Next, two studies of primary data in an early psychosis sample were completed to look at specific, hypothesized relationships between the sub-components of premorbid adjustment and sub-domains of social, occupational, and global functioning.

The systematic review provided an update to a previous review by MacBeth and Gumley (2008). This previous review only included global psychosocial functioning as the outcome and used methodologically problematic scales. Multiple measures of premorbid functioning were used, making comparison difficult across scales. Only 10 studies with mixed diagnostic groups were included in the previous study. The new systematic review identified 14 new studies who used the premorbid functioning data beyond an overall score, with two approaches identified primarily, by domain or by development stage. Social premorbid functioning and late adolescence development stage proved to have the most support for relationship to subsequent psychosocial outcomes in longitudinal

investigations up to 8 years. These findings support the relationship between premorbid functioning to post-onset psychosocial functioning across sub-domains. However, a gap in the literature was identified as no single study utilized a domain by trajectory analytic approach, setting the stage for the primary data investigations.

To address the previously identified gap in this line of work, a comprehensive domain by trajectory analytic approach of premorbid functioning was explored in relationship to social, occupational, and global psychosocial functioning at baseline or study entry and at two-year follow-up. Study entry results in the current longitudinal sample provided further support for findings from the systematic review, but this was the first study of its kind to use the full range of premorbid variables to predict psychosocial functioning by sub-domains in early psychosis. We found significant models for both social and global psychosocial functioning at study entry but not for occupational functioning. Interestingly, the trajectory of social development during the premorbid period was associated with both global and social functioning. Initial level of social performance was also associated with social performance while initial level of academic performance was associated with global functioning. These results, taken together, are illustrative of these consistently related relationships, and may be utilized in future psychosocial intervention studies.

The relationship between premorbid adjustment and psychosocial outcomes at two-year follow-up were examined to determine if these patterns are present at longer follow-up in the illness course. Despite a smaller sample size, models for global, social, and occupational two-year psychosocial functioning were significant. Two-year global and occupational functioning was predicted by initial academic level and academic trajectory while two-year social functioning was predicted by initial social performance and trajectory over time and initial academic level. These results are encouraging and suggest the strength of these relationships increase with more distal outcomes.

A secondary question for this project was the impact of demographic variables on the identified relationships. While we were underpowered to include these as a variable in the regression models, we did find group differences by gender and race. At study entry, female sex was identified as a potential protective factor as women had higher initial academic performance in childhood, improving social trajectory throughout development, and higher global psychosocial functioning. At two-year follow-up, differences by racial group were found in post-onset social functioning such that those belonging to a non-white racial group were significantly lower in social functioning than their white counterparts. These results highlights a potential areas for follow-up studies to see if these findings are replicated. Further understanding the contributing factors to these differences based on gender or racial category are an important next endeavor for future studies.

Overall, the results of the three studies included in this dissertation point to a consistent pattern between premorbid adjustment and post-onset psychosocial functioning in the early stages of psychosis and longitudinally throughout the illness course. Future studies are needed from various research groups using the full range of premorbid variables available to establish a clear understanding of these patterns to post-onset psychosocial functioning. Replications including longer term follow-up and in well powered and demographically balanced samples are needed to strengthen our certainty in these findings. However, the most important recommendation is that any study that utilizes the PAS for should use operationalized variables that include domain by developmental approach rather than an overall average or averages at each domain or development stage.

The PAS is widely used in schizophrenia research, and until now, many studies have chosen a limited approach to this rich developmental data. The most valuable future direction from this line of research is for its use both clinically in practice and in future intervention research studies. Premorbid adjustment patterns provide rich data about an individual's academic or social strengths and challenges before the illness begins, providing insight into functional abilities before the disorder interferes and

disrupts these activities. This information is highly useful for future psychosocial rehabilitation interventions that may be tailored to individuals based on their pre-illness background. For example, particularly for interventions such as cognitive remediation, supported education and employment, and social skills training, premorbid patterns can be helpful in setting treatment goals and understanding pre-illness strengths or challenges. More individually tailored goal setting based on who the person was and what they were able to accomplish before the illness sets in and masks many of these areas, would be an improvement for recovery focused interventions. Clinicians treating psychotic patients in the clinic or inpatient settings may also find this relatively quick and easy to use rating scale of value in setting treatment goals beyond what may be recovery goals at first glance. As many patients and families impacted by this serious mental illness often share, the ultimate goal for patients with psychosis is to return to their pre-illness functional levels in order to carry on and lead satisfying, independent lives. These premorbid markers from the PAS are a good step to provide this information quantitatively for treatment planning and tailoring of rehabilitative treatments in support of recovery efforts in psychosis.

The results of this work point to some suggested policy implications. The search to identify a cause of schizophrenia or predict who will go on to develop schizophrenia has been largely unsuccessful although researchers have information regarding a large range of prognostic features. Despite this lack of predictive ability, we can bolster support services and assessment throughout development to attempt preventative measures for developing psychotic disorders. Wide-ranging, routine testing of both social and academic functioning for children and adolescents would increase the chances of identifying students suffering from a host of potential mental health concerns, even beyond psychosis. A standardized assessment that includes psychosocial functioning and brief, neuropsychological or cognitive testing, would not only characterize how students are progressing along to identify any needs in the moment, but also provides critical information throughout their lives that can be shared with treatment providers and families when discussing trajectories of functioning and individualized goal

setting and treatment services where necessary. Local, state, and federal policy implications for routine, standardized assessment of cognitive and social performance, will highlight chances at preventative strategies for psychotic and other mental health disorders while providing important information for researchers and treatment providers for the future. Any steps that could be reasonably taken to assist in preventative strategies for psychosis and other mental health disorders should be a high priority for society as easing the burden brought on by severe and persistent mental health disorders is imperative. Recovery efforts in psychosis are critical, but preventative measures that could be taken should be the focus of policy plans and funding priorities.

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VITA

Kristan Armstrong received her Bachelor's degree in Psychology from Maryville College in Maryville, Tennessee. She then began work at Vanderbilt University Medical Center (VUMC) in the Department of Psychiatry in the Psychiatric Neuroimaging Program. This provided inspiration to pursue a Master's degree in Social Work from the University of Tennessee, College of Social Work, Nashville campus. From clinical internships and clinical work at Vanderbilt, she became an experienced social worker with a focus on severe and persistent mental health disorders, with schizophrenia and psychotic disorders as a specialty area. Her work continued on the inpatient unit and outpatient clinics with early psychosis patients at VUMC while managing a longitudinal neuroimaging study in this population. This intersection of clinical work and research led her to pursue her doctorate in Social Work. Her research interests include predicting psychosocial outcomes in early psychosis, recovery oriented interventions for psychosocial treatment, and linking clinical predictors to brain based understandings of psychosis. After graduation, Kristan will remain a faculty member at Vanderbilt Medical Center in the Department of Psychiatry conducting clinically informed research with longitudinal investigations of early psychosis patients. She is incredibly appreciative of all the support from her family, friends, colleagues, and partner.