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Attention Deficit/Hyperactivity Disorder in Youth at Clinical Risk for Psychosis: Childhood Functioning, Familial Mental Illness, and Current Symptoms

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By

Katrina Goines
B.Sc.(Hons), University of Cape Town 2009

Advisor: Elaine F. Walker, Ph.D.

An abstract of
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Abstract

Attention Deficit/Hyperactivity Disorder in Youth at Clinical Risk for Psychosis: Childhood Functioning, Familial Mental Illness, and Current Symptoms
By: Katrina Goines

Attention Deficit/Hyperactivity Disorder (ADHD) is one of the most commonly diagnosed childhood disorders in those who go on to develop psychosis. Familial risk studies also consistently report high prevalence of ADHD among the family members of individuals with a psychotic disorder. Despite multiple theories attempting to account for the comorbidity between ADHD and psychosis, the meaning of the ADHD-psychosis association remains unclear. The present study investigated potential clinical correlates of ADHD in a sample of youth at clinical high risk (CHR) for psychosis. A CHR group with a previous ADHD diagnosis was compared to a matched CHR group without an ADHD diagnosis in terms of severity of prodromal symptoms, impairments in childhood functioning, and the presence of a family history of mental illness. Due to recent studies indicating that sex may moderate the relation between ADHD and psychosis, exploratory analyses aimed at identifying differential effects of sex were also conducted. All data were gathered during a baseline clinical interview. Results revealed that ADHD was associated with significantly more severe disorganized prodromal symptoms and a trend towards more severe positive symptoms when compared with the non-ADHD group. Additionally, ADHD was associated with significantly more impaired academic functioning that began early in childhood and remained consistently impaired throughout adolescence. ADHD was not associated with more impaired social functioning compared to the CHR non-ADHD group. Finally, ADHD was also associated with a greater family history of mental illness, and exploratory analyses revealed that this effect differed by sex of the participant. Specifically, relatives with psychosis were found to be 6.7 times more common in ADHD females compared to non-ADHD females, and relatives with depression were found to be twice as common in males with ADHD when compared to males without ADHD. Overall, findings provide support for theories of a specific subtype of psychosis characterized by both early symptoms of ADHD and a familial liability for psychosis. Findings also highlight the need for additional investigations into the role of biological sex in ADHD-psychosis relations.

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Attention Deficit/Hyperactivity Disorder in Youth at Clinical Risk for Psychosis: Childhood Functioning, Familial Mental Illness, and Current Symptoms

Schizophrenia and other psychotic disorders are serious and debilitating conditions that affect about 1-2% of the population world-wide and are associated with costs of over $62 billion a year in the U.S. alone (Wu et al., 2005). The causes and etiology of these disorders are complex and heterogeneous, and are still not well understood. Schizophrenia is typically associated with a decline in cognitive and social functions, as well as with extensive psychotropic medication use, making controlled study of the disorder difficult. Consequently, much of the recent work investigating etiology has focused on the period before onset of psychosis, known as the prodrome to psychosis.

The psychosis prodrome is defined by the presence of attenuated psychotic symptoms that immediately precede the onset of a psychotic illness. This period may last anywhere from a few months to a few years and is believed to be an optimal period in which to study the precursors and predictors of psychotic illnesses (McGlashan, 1998), as well as being an ideal time for preventative intervention efforts (Addington & Heinssen, 2012). It is well established that psychotic syndromes are associated with a variety of symptom profiles, and they are generally believed to be similarly heterogeneous in terms of etiology. Thus, research aimed at understanding etiology has begun to focus on identifying potential subgroups whose more homogeneous presentation may be associated with similar etiological factors. A better understanding of the precursors and risk factors at play during the prodrome to psychosis may better facilitate the identification of etiologic subtypes and lead to enhanced prediction and prevention efforts at the earliest stages of illness.

Defining Risk for Psychosis

Since the prodrome to psychosis can only be accurately defined retrospectively, after an individual has met full diagnostic criteria for a psychotic disorder, it is not possible to prospectively recruit "prodromal" individuals in order to study their conversion to psychosis. Researchers interested in the prodromal period typically aim to recruit 'high risk' individuals, or those who are considered more likely to convert to a psychotic illness than individuals from the general population. Different strategies for identifying and recruiting such high risk individuals have been associated with varied levels of success. One common strategy is to define a high risk individual as someone who reports having one or more family members with a psychotic illness. In the literature, this type of high risk group is termed "Genetic High Risk (GHR)" or "Familial High Risk (FHR)" and is based on the fact that psychotic disorders like schizophrenia have substantial heritability (up to about 70% heritability according to Kendler & Diel, 1993) and, as such, those with the 'genes' for psychosis are more likely to convert to a psychotic illness at some point in their life. However, FHR samples typically report low rates of conversion and low positive predictive values (McGorry et al., 2003).

Another strategy that has proved more efficient at identifying those at risk of psychosis is the "Clinical High Risk (CHR)" strategy. Clinical High Risk is defined not by a hypothesized familial liability for psychosis, but instead on the basis of the presence of attenuated psychotic symptoms expected during the prodrome to psychosis. For example, a psychotic symptom such as visual hallucinations, is often preceded by attenuated psychotic symptoms such as visual illusions or distortions that the individual often finds puzzling and concerning. These 'sub threshold' psychotic symptoms are typically experienced with some degree of skepticism on the part of the individual, who does not fully believe that the experience occurred in reality. For ease

of communication, these symptoms will be called "prodromal" symptoms for the remainder of this paper, with the knowledge that this is not entirely accurate due to retrospective nature of the prodrome as a definition. Clinical high risk samples are associated with a conversion rate of 29% over two years (Fusar-Poli et al., 2012), making them preferable to FHR samples empirical questions regarding the prodrome to psychosis.

ADHD and Risk for Psychosis

Research has shown that those who develop a psychotic illness often show signs of developmental and social impairment well before they can be even considered prodromal (e.g., Schiffman et al., 2004). Additionally, those who go on to develop psychosis frequently report a history of childhood psychological disorders (Keshavan et al., 2011). ADHD is one such disorder that is commonly diagnosed in those who go on to develop psychosis (Kim-Cohen et al., 2003).

Prevalence rates of ADHD within schizophrenia and first-episode psychosis samples are consistently high (Rubino et al., 2009; Karatekin et al., 2010; Peralta et al., 2011), and some studies of early onset schizophrenia have reported prevalence rates as high as 82% (Ross et al., 2006) and 66% (Karatekin et al., 2010). These values are considerably larger than global estimates of ADHD prevalence, which are reported to be around 5-6% (Polanczyk et al., 2007). Additionally, ADHD has been found to be one of the most common disorders of childhood and adolescence experienced by people who go on to develop schizophrenia (Kim-Cohen et al., 2003). Although the risk of developing psychosis increases after any childhood disorder (Maibing et al., 2014), there is some evidence to suggest that a diagnosis of ADHD is specifically associated with risk for psychosis disorders (Hickie et al., 2013; Rubino et al., 2009). This is not only true for affective psychoses, such as bipolar disorder, which is frequently associated with ADHD (e.g., Duffy, 2012). Recent studies have found that ADHD is equally as

prevalent prior to schizophrenia as prior to bipolar disorder (Andersen et al., 2013; Dalteg et al., 2014). These and other findings (e.g., Hamshere et al., 2013; Hill et al., 2013; Stahlberg et al., 2004) suggest that ADHD or symptoms of attentional problems in youth may indicate a vulnerability to psychosis generally, rather than being either bipolar- or schizophrenia-specific.

Recently, two studies assessing relative risk of schizophrenia concluded that children with ADHD were at a significantly increased risk for developing schizophrenia (RR=4.3; Dalsgaard et al., 2014) (RR ~ 5; Dalteg, 2014). In both studies, this risk ratio was far greater for ADHD females diagnosed compared to female controls, than it was for the ADHD males compared to controls (RR for females = 20.1; RR for males = 2.9; Dalsgaard et al., 2014). These findings suggest that an ADHD diagnosis in childhood confers heightened risk for later psychosis in both sexes, and additionally that sex may moderate the effect between ADHD and psychosis. Dalsgaard's group even suggests that clinicians should be advised to monitor childhood ADHD cases for the possibility of progression towards psychosis.

Overall, it appears that there is robust evidence of comorbidity between ADHD and psychosis (for a more comprehensive review see Pallanti & Salerno, 2015). There is also evidence that ADHD is linked with greater risk for conversion to psychotic illness, indicating the potential clinical significance of this comorbidity. Since ADHD is typically first identified in childhood, examination of the relations between ADHD and psychosis syndromes may enhance our understanding the earliest stages of risk and the developmental divergence of subtypes of psychosis. Additionally, individuals being diagnosed with ADHD are typically young, help seeking, and under the care of a medical provider, making them an ideal group for potential early intervention efforts.

Models of ADHD-Psychosis Relations

A review of the literature reveals multiple different theories that have been offered to account for the ADHD-psychosis association, some of which are discussed below.

Shared Etiologic Risk Factors: ADHD and psychosis share similar environmental risk factors including low birth weight, prenatal insults (e.g., maternal malnutrition, substance abuse, stress exposure), and obstetric complications (Abel et al., 2010; Linnet et al., 2003; Peralta et al., 2011). Both disorders are also associated with varying degrees of developmental delay (Owen et al., 2011). One of the more parsimonious theories on the ADHD-psychosis relation is that the two disorders co-occur inevitably, simply as a result of sharing common risk factors. Peralta and colleagues (2011) proposed this theory in a report on results from their study of first episode psychosis. In it, they that concluded that childhood ADHD in those with later psychosis was simply an epiphenomenon of obstetric complications that resulted in early neurodevelopmental delays with no further effect on clinical presentation. While the specific finding that ADHD and psychosis are related through obstetric complications alone has yet to be replicated in a different sample, the general theory that shared risk factors may lead to a vulnerability for both disorders seems plausible. It is easy to imagine how any of the previously described risk factors may connote some general liability for neurodevelopmental disorders that is expressed differently at different stages of development. Early attention problems may be particularly noticeable around school age, whereas changes in hormones and increasing demands during adolescence may uncover additional impairments that are more characteristic of psychosis.

While Peralta's previously mentioned theory focused solely on shared environmental risk factors, another emerging theory is that ADHD and psychosis are related through some shared genetic liability for the two disorders (see *ADHD as a Familial Marker of Risk of Psychosis*). Of

course, genetic and environmental risk factors are not mutually exclusive groups, and in some cases may not even be easily separable. For example, there is evidence that obstetric complications occur more frequently in those who have a genetic risk for psychosis than those without (Preti et al., 2012), indicating how genes and environment may interact to produce a hypothesized underlying vulnerability for both ADHD and psychosis.

Drug use in ADHD increases risk for psychosis: Individuals with ADHD are known to be more prone to illicit drug use and abuse than those without ADHD (Gudjonsson et al., 2012). Drug use is also very common among those with a psychotic illness, as well as those at risk for psychosis (Buchy et al., 2015). While illicit drug use has been linked with the onset of a psychotic illness (Cassidy et al., 2011), the causal role of illicit drug use on psychosis is still debated. Overall, it seems that while illicit drugs such as cannabis are neither necessary nor sufficient to cause psychosis, they likely increase risk for psychosis (Arseneault et al., 2004), and the increased risks of psychosis conferred by drug use may be one factor responsible for the ADHD-psychosis association.

It has also been suggested that prescription stimulant usage among those with ADHD may put these individuals at risk for developing psychosis (Ross, 2006). One study reported that 77% of youth with psychosis had been exposed to stimulants (Schaeffer et al., 2002) and another found the age of onset of psychosis to be younger in those with psychostimulant exposure (Karatekin et al., 2010). There are also a multitude of case studies and anecdotal reports of individuals who developed psychotic-like symptoms after taking stimulant medication. However, there are also studies that have found little or no relation between psychosis and stimulant medication, and some that have concluded stimulants are associated with favorable outcomes in those with psychosis in terms of cognitive (Barch et al., 2005) and negative symptoms of

psychosis (Lindenmayer et al., 2013). In summarizing the literature, it seems that while large doses of stimulants such as amphetamines can induce brief psychotic symptoms, therapeutic doses can be beneficial if psychosis is already stabilized (Curran et al., 2004). However, due to the lack of studies of stimulant usage in youth at high risk of psychosis, the theory that stimulants may mediate the onset of psychosis in this group cannot be dismissed.

Severity Continuum: Since attentional dysfunction often co-occurs with psychotic symptoms, one frequently mentioned theory is that ADHD prior to psychosis may simply be a marker of severity (Karatekin et al., 2010; Peralta et al., 2011), such that those with more severe attentional symptoms will also display more severe psychotic symptoms. While it is intuitively appealing, this theory has been generally discredited by evidence that those with ADHD prior to psychosis do not tend to show greater psychotic symptom severity in all domains when compared with those who did not have ADHD prior to psychosis (Keshavan et al., 2003, 2008; Niemi et al., 2003; Peralta et al, 2011). In fact, the robust finding in the literature is that those with severe attention dysfunction display more severe negative symptoms of psychosis, but not more severe positive symptoms of psychosis (Addington et al., 1991; Clark et al., 2010; Moritz et al., 2001; Norman et al., 1997). This suggests that the impairments associated with an ADHD diagnosis prior to psychosis are specific and cannot be characterized by greater severity across the board.

Misdiagnosis: Another way of understanding the ADHD-psychosis comorbidity is to assume that attentional dysfunction is a very early symptom of psychosis, and that ADHD is actually a misdiagnosis when it is followed by a psychotic disorder (Seidman et al., 2013). This theory would suggest that early attentional deficits reflect a diathesis for psychosis, which gets labeled as ADHD before the full expression of psychotic vulnerability becomes visible later in adolescence or young adulthood. However, it is as yet unknown whether there is any way to

differentiate this type of individual at the time of ADHD diagnosis from the majority of individuals with ADHD who never develop psychosis. Additionally, if at the time of the ADHD diagnosis, the individual is not expressing any symptoms of a psychotic disorder, then it is unclear what the "correct" diagnosis could be.

Etiological/Development Subtype: As early as 1987, Bellack coined the term 'ADHD-psychosis' to refer to this group of patients whom he believed represented a subgroup of schizophrenia characterized by paucity of hallucinations, affective blunting, low frustration tolerance, mild formal thought disorder, poor impulse control, and restlessness. Elman and colleagues (1998) found partial support for the ADHD-psychosis subgroup theory in their investigation of ADHD in childhood-onset schizophrenia. They added that ADHD was indicative of a subgroup of psychosis with a more insidious course of illness and poorer response to neuroleptic medication. Studies of neuropsychological correlates of psychosis have quite consistently found associations between high levels of executive dysfunction (a major symptom of ADHD), and high levels of negative and disorganized symptoms (Clark et al., 2010; Donohoe et al., 2006; Moritz et al., 2001). In the literature, more severe negative symptoms are often associated with a poorer response to medication and overall poorer functioning outcomes (Kirkpatrick, 2014). Additionally, there is evidence that in the general population, ADHD is associated with more symptoms of thought disorders (Caplan et al., 2001). Taken together, these pieces of evidence provide some theoretical support for the theory that ADHD-psychosis may represent a subtype characterized by greater attentional and cognitive deficits, greater severity of negative symptoms and disorganized symptoms, thought disorder, poorer response to medication, and poorer outcomes. However, some later studies on the clinical correlates of ADHD in psychosis have found no significant differences in positive or negative symptoms, or

other relevant clinical correlates that would suggest an ADHD-psychosis subtype (Karatekin et al., 2010; Peralta et al., 2011). Empirical support for this theory remains mixed.

ADHD as a Familial Marker of Risk for Psychosis

Studies focused on relatives of those with schizophrenia have frequently found that those relatives are more likely to report childhood symptoms of ADHD than individuals in the general population (Niemi et al., 2003). In fact, most familial high risk studies of psychosis report ADHD prevalence rates at around 20 – 25% of relatives (Keshavan et al., 2003, 2008; Oner & Munir, 2005). This has led some investigators to hypothesize that elevated rates of ADHD and attentional dysfunction in family members may indicate a genetically inherited vulnerability to psychosis (Keshavan et al., 2003). In line with this theory, a recent study by Dickson and colleagues (2014) found a dose-dependent relationship between familial load for psychosis and resulting executive function impairments. Together, these findings suggest that a vulnerability for ADHD may be inherited along with a familial vulnerability for psychosis.

Additionally, there is research suggesting that the attention dysfunction may be predictive of conversion to psychosis when found in FHR samples (Erlenmeyer-Kimling et al., 2000; Mirsky et al., 1995). Furthermore, other findings suggest that in FHR samples, a combination of ADHD-like symptoms and schizotypal traits (or other prodromal symptoms) may enhance predictions of conversion to psychosis (Keshavan et al., 2003, 2008). A review of the literature revealed no studies of the association between ADHD and conversion to psychosis in a CHR sample, but some have investigated specific neurocognitive functions as predictors of conversion. Those studies investigating sustained attention have concluded that sustained attention does not predict conversion in CHR samples, but is likely a stable marker of vulnerability for psychosis (i.e., the impairment is present premorbidly and does not worsen

significantly following onset of psychosis) (Lencz et al., 2006; Francey et al., 2005). Taken together, this may suggest that ADHD and attentional dysfunction are markers that are more closely associated with a familial risk for psychosis than a clinical risk. However, as of yet there are no known studies investigating the relation between CHR and ADHD.

Present Study and Hypotheses

The present study seeks to investigate the potential relation between ADHD and certain hypothesized clinical correlates within a CHR sample. Specifically, severity of prodromal symptoms, childhood functioning, and family history of psychosis will be analyzed and compared in CHR groups with and without a diagnosis of ADHD. As previously discussed, examining the potential etiological/developmental subtypes within the prodromal period has the potential to reveal important information that can be used inform prediction and early intervention efforts. Current theories of the ADHD-psychosis association will also be evaluated in light of the findings. The aims of the study are as follows:

1. Differences in psychotic symptom severity between the CHR ADHD and CHR no-ADHD group will be investigated. Based on findings from neuropsychological literature (Clark et al., 2010, Donohoe et al., 2002) it is hypothesized that the ADHD group will manifest greater severity of negative and disorganized symptoms.
2. Potential group differences in the developmental trajectory of psychotic illness will also be investigated by examining scores on premorbid functioning measures. It is hypothesized that the ADHD group will endorse more severe functioning impairments than the non-ADHD group. Additionally, potential group differences in specific domains of functioning will be explored.

3. Family history will be examined as it relates to ADHD within the CHR group. Based on findings from FHR studies, it is hypothesized that ADHD will be associated with a family history of psychosis. It is further hypothesized that ADHD will be more strongly associated with a family history of psychosis than with a family history of depression.

Exploratory aim: Due to recent evidence that sex may act as a moderator in the relation between ADHD and psychosis (Dalsgaard et al., 2014, Dalteg et al., 2014), analyses aimed at exploring this possibility will also be conducted.

Method

Participants

The sample was drawn from participants recruited for a multisite collaboration called the North American Prodromal Longitudinal Study II (NAPLS II) (for recruitment and study procedures see Addington et al., 2012). All participants were in the 12 to 35 year age range and were screened to exclude those with traumatic brain injury, neurological disorders, recent substance dependence, or a Full Scale IQ below 70. At the time of the analysis, there were a total of 743 CHR participants with data about ADHD diagnoses. A group of CHR participants with ADHD was identified and compared to those without ADHD on a number of demographics including sex, age, race, and years of education. Independent Samples T-tests revealed that the groups differed significantly in terms of age ($p<0.001$), with the ADHD group being younger on average than the non-ADHD group ($M=17.55$ vs. $M=18.79$). Chi-squared analyses also revealed significant differences in race between ADHD and non-ADHD CHR groups ($p<0.001$), such that the ADHD group was composed of greater numbers of individuals from minority groups (especially First Nations, and Hispanic groups). For each ADHD positive CHR subject, a same-sex, same-race, nearest-in-age CHR subject with no history of ADHD was selected. The

resulting two groups (ADHD N=163, non-ADHD N=163) did not differ on sex, race, age, or education. All following analyses included only participants with full data on the variables of interest. This resulted in some minor variations in sample size for each analysis.

Measures

Prodromal Symptoms. The *Structured Interview for Prodromal Syndromes* (SIPS) (Miller et al., 1999) is a reliable and valid (Miller et al., 2003) semi-structured interview used to assess prodromal symptoms and determine if individuals meet the Criteria of Prodromal Syndromes. An individual who meets these criteria is considered "CHR" status for our study. A six-point scale (0 to 6) is used to rate individual symptoms and reflects severity, frequency, duration, and intensity and/or degree of conviction. The semi-structured interview assesses five specific positive symptoms, six negative symptoms, four disorganized symptoms, and four general symptoms. Averaging all scores within a particular symptom domain derives one composite score for each major symptom type. Designation as CHR is based on scores from the positive symptom domain. Scores from zero to two reflect what is considered to be normal/sub prodromal symptomatology, three to five indicates a prodromal level of symptomatology/CHR status, and scores of six suggest the possibility of a psychotic state.

ADHD Status. The *Structured Clinical Interview for DSM-IV Axis I Disorders* (SCID-IV) (First, Spitzer, Gibbon, & Williams, 2002) is a semi-structured interview designed to verify and categorize the presence of Axis I disorders according to DSM-IV criteria. This was administered during the initial interview to confirm a history of ADHD and any other Axis I diagnosis in the NAPLS participants.

Developmental Trajectory. The Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982) is a self-report questionnaire that was administered to participants in an interview format

to assess psychosocial, academic and personal functioning at various developmental stages from childhood to adulthood. It consists of a rating scale made up of 6 items with high scores indicating greater impairments in functioning. When necessary, due to subjects' young age or difficulty remembering, information from caregivers/parents was also utilized to complete the questionnaire. Due to the young age of some participants, only the childhood, young adolescent, and older adolescent portions (which encompasses ratings from before 11 years to 18 yrs.) of the scale were used in the present research, as it is the adult portion is incomplete for many participants.

Family History. The Family Interview for Genetics Studies (FIGS) (Maxwell, 1992) is a semi-structured interview used to record all first and second degree relatives of the participant and rate whether each relative had a specific psychological disorder (categories are depression, mania, schizophrenia, or other psychosis). For each category, family members are rated 'no', 'unknown', 'probably', or 'definitely' depending on the participant's response to specific prompts about that family member. For the current study, the variable of interest was family history of psychosis generally, so the 'schizophrenia' and 'other psychosis' categories were merged for the purposes of this study. The full family member ratings were converted into a count variable for each participant indicating the number of first-degree relatives that participant has with each type mental illness (e.g., number of first degree relatives with psychosis, number of first degree relatives with mania, number of first degree relatives with depression).

Procedures

The same study procedures took place at each of the NAPLS sites and all interviewers underwent reliability trainings and checks before conducting interviews. After an initial screening, using the SIPS and SCID-IV to determine eligibility for the study, participants then

returned for a baseline interview during which additional clinical measures were administered. All data for the present analysis was gathered at baseline for all participants.

Analytic Strategy & Preliminary Analyses

The plan for each analysis is described below. All analyses were performed using IBM SPSS 21.0.

Analysis 1: The aim of this analysis was to compare ADHD and non-ADHD groups in terms of their symptom severity in four different symptom domains. A MANOVA was performed with ADHD status as the independent variable and composite scores of positive, negative, disorganized, and general symptoms as the separate dependent variables. After natural log (x+1) transformation, the dependent variables and residuals were approximately normally distributed in both groups. Correlational analyses revealed that dependent variables were moderately correlated (around r=0.4) in each group. Levene's test revealed that homogeneity of variance can be assumed for all dependent variables in each group.

Analysis 2: The aim for this analysis was to compare the trajectory of premorbid functioning impairments between ADHD and non-ADHD groups, across development. This analysis utilized a mixed design ANOVA with ADHD status as the independent, between groups variable. The analysis included a repeated measures design of three different domains of functioning (i.e., Sociability, Peer Relations, Scholastic Achievement) over three different developmental periods (i.e., childhood up to 11 years, 12-15 years, 16-18 years). After log10 (x +1) transformation, these data and residuals were approximately normally distributed for all dependent variables at each level of the independent variable. According to Mauchly's sphericity test, the effects violate the assumption of sphericity; so all effects were interpreted using the

Greenhouse-Geisser correction. According to Levene's test, the data exhibited homogeneity of variance across all levels of the repeated measures variables.

Analysis 3: The aim of this analysis was to identify whether a family history of psychosis was more prevalent in the ADHD group than the non-ADHD group. Additionally, prevalence of family history other disorders (depression, mania) was also analyzed between groups. The positively skewed distribution that is present in count or frequency data of less common events (e.g., having a family member with psychosis) required analysis using tests that do not assume a normal distribution. A Poisson or negative binomial distribution appeared to be more appropriate for this data and when compared with a Poisson regression model, goodness of fit statistics indicated that the Negative Binomial model was a better fit the data (e.g., Poisson BIC = 599.800; Negative Binomial BIC = 502.539). Therefore, three separate simple negative binomial regressions were performed with ADHD status as the predictor variable and number of first degree family members with each specific mental illness as the three separate outcome variables (i.e., ADHD status was regressed on number of family members with psychosis, then again on number of family members with mania, and finally on number of family members with depression). Total number of first-degree family members was set as the offset variable indicating the number of possible 'exposures' (i.e. family members) for each 'hit' (i.e., occurrence of a family member with psychosis).

Exploratory Analysis: All previous analyses were repeated separately for each sex. Splitting the sample first by ADHD group and then by sex resulted in smaller sample sizes per group (smallest was females with ADHD, N=50), so analyses should be interpreted with caution. This is especially relevant for the negative binomial regression analysis, as this test is not appropriate for small samples. Additionally, for the first two analyses, the sex-separated data

were typically less normally distributed than the data from the original two groups. However, since the violations of normality were not extreme, these data were not re-transformed. While these decisions were deemed appropriate for these preliminary explorations, they should be kept in mind during interpretation of the results.

Results

Demographic Characteristics

Twenty-two percent of the entire CHR sample was identified was having a diagnosis of ADHD. This is consistent with reports of ADHD in about a quarter of most FHR samples (Peralta et al., 2011). In the matched samples, both the CHR ADHD and the CHR groups were majority male (Table 1.), which is expected given that both CHR and ADHD samples are typically comprised of larger percentages of males. After matching samples, the ADHD and non-ADHD groups did not differ on age, race, or sex. Antipsychotic medications were being used by 16.6% of the ADHD sample and 14.7% of the non-ADHD sample. Stimulant medication use was restricted to the ADHD group and characterized 19% of the ADHD group.

As a validity check, the relation between ADHD status and self-reported attentional problems (using symptom D3 from the SIPS: “Trouble with Focus and Attention”) was examined using an Independent T-test. Trouble with Focus and Attention was found to be significantly different between groups ($F(1, 322)=3.470$; $p<0.001$), with the ADHD group endorsing higher severity of attention symptoms (ADHD M=3.23, non-ADHD M=2.48). A T-test comparing a cognitive measure of inattention, the Continuous Performance Task (CPT-IP), also revealed significant group differences ($F(1,292)=0.031$, $p=0.048$), with the ADHD group achieving a lower mean T-score than the non-ADHD (ADHD M=34.96, non-ADHD M=37.93). These results indicate that the measure of ADHD used in this study has validity.

Analysis 1

Using Pillai's trace, the MANOVA revealed a significant effect of ADHD on severity of prodromal symptoms [$F(4,303)=5.643$, $p<0.001$]. Separate univariate analyses presented in Table 2. revealed significant group differences in disorganized symptoms severity only [$F(1,306)=18.86$, $p<0.001$]. Group differences in positive symptoms were near significance [$F(1,306)=3.097$, $p=0.079$]. In both cases, the direction of difference was such that the ADHD group endorsed more severe symptoms than the non-ADHD group. Preliminary analyses demonstrated that the ADHD group was rated as significantly more severe on the symptom of "Trouble with Focus and Attention" (symptom D3), so the analysis was repeated with this symptom removed. As can seen on Table 3., the same pattern of differences remained even when D3 was removed from the analysis.

Separate Sex Analyses

This analysis was then repeated separately for each sex. Results, presented in Table 4., revealed that the omnibus MANOVA was significant for both sexes. Univariate analyses revealed that the only significant group difference for females was in disorganized symptoms, whereas males exhibited significant group differences for both positive and disorganized symptoms.

Analysis 2

Main Effects

There was a significant main effect of ADHD status [$F(1, 202)=4.305$, $p=0.039$], in which the ADHD group generally endorsed a greater degree of impairment in functioning (ADHD M=0.419, non-ADHD M=0.373). There was also a significant main effect of time [$F(1.876, 378.977)=15.839$, $p<0.001$]. Contrasts revealed a significant difference between ratings

of the earliest developmental period (childhood up to 11 years) and the latest developmental period (16-18 years)[$F(1.876, 202)=22.258$, $p<0.001$] with the ratings at the older ages revealing greater overall impairments in functioning. This indicates that on average, this CHR sample endorsed more severe functional impairments at the later developmental stages than the earliest, without taking ADHD status into account. This makes sense given that the later time period corresponds to the age at which many of the individuals are experiencing various prodromal symptoms.

There was also a significant main effect of domain of functioning [$F(1.755, 354.525)=46.993$, $p<0.001$]. Contrasts revealed that impairments in scholastic performance were significantly more severe than impairments in either sociability [$F(1, 202)=27.813$, $p<0.001$] or peer relations [$F(1, 202)=81.971$, $p<0.001$]. The two ratings of social impairments were not significantly different from each other. This indicates that this CHR sample generally endorsed more severe impairments in scholastic than social domains.

Interaction Effects

There was a significant interaction effect between the developmental time period and domain of functioning [$F(3.270, 660.56) =16.293$, $p<0.001$]. This effect indicates that impairments in specific domains of functioning differed over time. Contrasts were performed comparing each domain of functioning to another across different developmental periods. The first contrast revealed a significant interaction when comparing the domains of peer relations and scholastic achievement at the first and last developmental periods [$F(1,202)=36.772$, $p<0.01$], and revealed that as development progressed, scholastic achievement impairments became more severe whereas peer relation impairments did not. The second contrast revealed the same direction of interaction effect at the second and third developmental time periods

[F(1,202)=5.801, p=0.017]. This indicates that whereas the social domain of peer relations did not appear to change in severity over time, the academic domain of scholastic performance seemed to be become more severely impaired across each period of development.

There was also a significant interaction effect between domain of functioning and ADHD status, F(1.76, 354.53)=6.17, p=0.004. This effect indicates that severity of impairments in specific domains of function differed according to whether or not the individual had ADHD. Contrasts were performed and revealed significant differences between ADHD and non-ADHD participants when comparing scholastic achievement to either sociability [F(1,202)=0.002] or peer relations [F(1,202)=0.024]. Estimated means analyses suggest that while the means for sociability and peer relations did not differ between groups, the ADHD group endorsed a particularly high level of impairment in scholastic achievement (M=0.540) compared to the non-ADHD group (M=0.428), and this may be the reason for the significant interaction.

The ADHD x domain of functioning x developmental time period interaction effect was not significant [F(3.270, 660.564)=1.832, p=0.135]. This indicates that the previously discussed ADHD-related differences in severity of impairment in specific domains did not change over time. Figure 1. is a graphical representation of this result showing that the ADHD group endorsed more severe mean values of impairment in scholastic achievement over all developmental time periods, compared to the non-ADHD group. In other words, whereas ADHD and non-ADHD groups did not differ in terms of social functioning, the ADHD group endorsed more severe impairments in scholastic achievement than the non-ADHD group. These impairments were present early in childhood and the ADHD group remained significantly more impaired in scholastic achievement across development, when compared to the non-ADHD group.

Separate Sex Analyses

When this analysis was repeated separately for each sex, results (presented in Table 6.) revealed a largely similar pattern of significant main and interaction effects between males and females, and both were similar to the results from the group as a whole. The one major difference between sexes was that for males, the main effect of ADHD was non-significant, whereas for females it was significant. This suggests that while the general pattern of effects is similar between sexes, for females, ADHD corresponds to a greater degree of impairment in premorbid functioning than in males.

Analysis 3

Family History of Mental Illness

As can be seen on Table 7., ADHD was found to be a significant predictor of number of family members with psychosis. The exponentiated coefficient [Exp(B)] was 2.256 indicating that CHR individuals with ADHD reported family members with psychosis at a rate of about double that of CHR individuals without ADHD. ADHD was also found to be a significant predictor of number of family members with mania. The Exp(B) of 1.825 indicates that on average, CHR individuals with ADHD report family members with mania at a rate of 1.8 times that of CHR individuals without ADHD. Finally, ADHD also was found to be a significant predictor of number of family members with depression. The Exp(B) of 1.509 indicates that on average, CHR individuals with ADHD report family with depression at a rate of 1.5 times that of CHR individuals without ADHD.

Separate Sex Analyses

Results from the separate sex analyses of family history are presented on Table 8. For males, ADHD status was *not* a significant predictor of number of family members with

psychosis. For females, ADHD *was* a significant predictor of number of family members with psychosis, and furthermore, it was associated with an exponentiated coefficient of 6.731. This indicates that on average, females with ADHD reported family members with psychosis at a rate of 6.7 times that of females without ADHD. For both males and females, ADHD was not a significant predictor of family history of mania in these separate analyses. For males, ADHD was a significant predictor of family history of depression and was associated with an exponentiated coefficient of 2.057. For females, ADHD was not a significant predictor of family history of depression.

Discussion

The present study sought to investigate clinically relevant differences between CHR individuals who did and did not have an ADHD diagnosis. Potential differences were examined in three different domains: prodromal symptom severity, developmental trajectory, and family history of psychotic and other disorders. Additional exploratory analyses were conducted to investigate whether sex differences within each group also impacted the relation between variables. Indeed, the results indicate that there are specific ADHD group differences in prodromal symptom severity, developmental trajectory, and family history for mental illness. Moreover, it appears that sex may play some moderating role in each of these effects, and may be especially associated with differential familial risk for mental illness within the ADHD group. Due to the indication that sex-related differences may be important for understanding the results from the three main analyses, the results of this exploratory analysis will be discussed along with each of the major ADHD-related findings below.

Differences in Prodromal Symptom Severity

Results from the MANOVA and follow-up univariate tests indicate that on average, CHR individuals with ADHD present with a different symptom profile than those without ADHD. Specifically, disorganized symptoms appear to be more severe in those with ADHD. In this analysis, the disorganized symptom domain includes separate symptoms of 'Odd Behavior and Appearance', 'Bizarre Thinking', 'Trouble with Focus and Attention', and 'Impairment in Personal Hygiene'. Even after removing the symptom 'Trouble with Focus and Attention' from the analysis, there was still a significant difference between groups on this domain. This indicates that the difference was not driven solely by the previously confirmed group differences on this single attention symptom. Additionally, results revealed marginally significant ADHD group differences in the positive symptom domain.

The separate sex analysis revealed differential results, such that ADHD males endorsed more severe positive and disorganized symptoms, whereas ADHD females endorsed more severe disorganized symptoms, compared to their same-sex non-ADHD group. It appears that the marginally significant difference in positive symptoms observed in the first analysis can be attributed to the males in the sample, but not the females. So overall, it seems that an ADHD diagnosis is associated with more severe disorganized symptoms 'across the board', and, for males only, ADHD is also associated with more severe positive symptoms.

These results provide partial support for the original hypothesis, in that disorganized symptoms were observed to be more severe in the ADHD group. However, no significant group differences were observed in the negative symptom domain, which runs counter to the original hypothesis that the ADHD group would endorse more severe negative symptoms. The lack of significant findings in difference of negative symptoms may be due in part to the inclusion criteria for this study. In order for an individual to meet CHR criteria, they must endorse

prodromal level severity (rated as a 3 to a 5 in the SIPS) in at least one positive prodromal symptom, but no such stipulation exists for the negative, disorganized, or general symptoms. Some previous studies have found that more severe executive dysfunction (Horan & Blanchard, 2003) and attentional impairments (Cohen & Doucherty, 2004) are associated with a "deficit syndrome" in which the individual's primary psychotic symptoms are longstanding negative symptoms. "Deficit syndrome" is also associated with poorer premorbid functioning, poorer outcomes, and less severe positive symptoms (Cohen & Doucherty, 2004; Kirkpatrick et al., 2001). Many of these individuals would not meet inclusion criteria for the present study due to their lack of severe positive symptoms. So it may be that the inclusion criteria, artificially limit the range of symptom expression that would typically associated with ADHD to only those with positive or mixed positive and negative symptoms, thereby decreasing the chance of observing a specific association between ADHD and negative symptoms.

On the other hand, while studies attempting to relate ADHD directly to psychotic symptoms have had mixed success (e.g., Peralta et al., 2011), neurocognitive studies have shown a robust association between attention and executive impairments and negative symptoms (for review, see Donohoe et al., 2003). So it may be that the diagnosis of ADHD, while clearly associated with impairments in sustained attention (as per the preliminary analyses in this study), does not fully account for variations in other theoretically associated constructs, such as executive functioning. This may occur for a variety of reasons including the well-documented bias that exists in ADHD diagnosis. Many factors are known to bias the diagnosis of ADHD including race (Morgan et al., 2013), sex (Bruchmuller et al., 2012), social-economic status and insurance status (Guerrero et al., 2011), and other comorbid disorders (Abikoff et al., 2002). So it is likely that a largely self-reported ADHD diagnosis is not sensitive enough to accurately

differentiate those experiencing more and less severe problems with attention and executive function. Incorporating neurocognitive measures of sustained attention and executive functioning will be important for future investigation in this area.

With regard to the finding of a significant ADHD-related difference in disorganized symptoms, it may be tempting to interpret this as confirmation that those with ADHD tend to be more disorganized than those without ADHD. However, it is important to note that the individual symptoms comprising the disorganized symptom domain are not simply a repeat of the types of symptoms required for an ADHD diagnosis. The symptoms within the disorganized symptom domain on the SIPS are more specific to the types of disorganized behavior characteristic of psychosis (e.g., trouble with personal hygiene, bizarre thinking) than ADHD. When removing 'Trouble with Focus and Attention', as was done for Analysis 1, the remaining symptoms do not directly correspond to any of the major symptoms of ADHD. However, it may still be the case that as a result of the disorganized cognitive processes present in ADHD, may report elevations in in this domain compared to those without ADHD. Yet again, it is also possible that only a combination of a pre-existing cognitive vulnerability (e.g., ADHD diagnosis) and emerging attenuated psychotic symptoms will result in this type of elevation on these psychosis-specific disorganized symptoms. Additional analyses including an ADHD, non-CHR control group may help to address this point.

Regardless of the reasons, the ADHD group does appear to endorse a different symptom profile in comparison to the non-ADHD group, and the ADHD symptom profile is characterized by more severe disorganized symptoms, regardless of sex. There are some potential clinical implications that are relevant to this finding. First, while much of the literature on functional outcome in psychosis has focused on the effects of negative symptoms (e.g., Ventura et al.,

2009), there is also evidence that disorganized symptoms are related to functional impairment in psychosis (Norman et al., 1999). Studies of high risk samples have also shown that disorganized symptoms at baseline are predictive of impaired social (Elsami et al., 2011, Carrion et al., 2013) and general functional outcome at follow-up evaluations (Demjaha et al., 2012; Ziermans et al., 2013). Second, while the evidence is mixed, there are some indications that in high risk individuals, disorganized symptoms may be predictive of transition to psychosis when combined with executive functioning deficits (Demjaha et al., 2012) or exposure to environmental risks for psychosis (e.g., trauma, urbanicity) (Saka et al., 2014).

With regard to the marginally significant group difference in positive symptoms, separate sex analyses suggest that this result was largely due to the males in the sample. Specifically, it appears that males with ADHD endorse more positive symptoms than males without ADHD. This is at odds with previous findings that those with more severe executive functioning impairments poorer attention tend to exhibit a greater severity of negative, but not positive symptoms (Addington et al., 1991, Moritz et al., 2001). However, there is also evidence that inattentive symptoms may be related psychotic-like experiences (PLE's), which are similar to sub-threshold positive symptoms of psychosis. Keshavan and colleagues (2003) found that in a FHR sample, those who exhibited higher ADHD symptoms also endorsed more magical thinking and perceptual aberrations. Studies of community samples have also reported higher levels of psychotic-like experiences in those with greater attentional impairment (Kelleher et al., 2013). Another recent study of psychotic-like experiences in a clinical sample found that individuals with ADHD reported positive psychotic-like experiences more frequently than individuals with other non-psychotic psychopathology (Rietdijk, 2014). However, it is still unclear why this association would exist for the males in the sample and not the females.

Alternatively, and perhaps most likely, it is also possible that the observed difference in positive symptoms was due largely to differences in the positive symptom of "Disorganized Communication". On the prodromal symptom measure used in this study (SIPS), Disorganized Communication is situated within the positive symptom domain and thus contributes to the positive symptom composite score. There is some debate as to whether this symptom measures attenuated thought disorder, which is thought to be a positive symptom, or whether it is more closely associated with cognitive symptoms such as sustained attention and organization/sequencing of speech (see Doucherty, 2005 for more details). It is possible that, at least within the ADHD sample, the Disorganized Communication symptom may be more related general disorganization and is thus more severely impaired in the ADHD group. Since males may on average have poorer verbal fluency than females (Hyde et al., 1988), it is possible that the additional impairments carried by an ADHD diagnosis may result in such significant deficits such that the male ADHD and non-ADHD groups are statistically significantly different on this single measure. Future research that includes follow-up analyses of specific symptoms may help to clarify this finding.

Differences in Developmental Trajectory

Overall, the results indicate that the ADHD group exhibited a different profile of premorbid functioning than the non-ADHD group. Specifically, the ADHD group endorsed severe impairments in scholastic achievement that were present from a young age and remained consistent throughout adolescent development. The separate sex analyses revealed a similar pattern of differences for both males and females over time. However, for males, the main effect of ADHD was not significant, whereas for females and the combined-sex group, the main effect of ADHD *was* significant. These findings provide support for the original hypothesis that the

ADHD group would endorse more severe impairments overall, and further adds evidence that ADHD prior to psychosis is characterized by a different trajectory of premorbid impairments.

Results of this analysis clearly showed that scholastic achievement was impaired in the ADHD group over and above whatever impairments exist in the non-ADHD CHR group. Additionally, these impairments were present from a young age (before 11 years old) and remained consistently poor throughout development in comparison to the non-ADHD CHR group. This finding has important implications as continuously poor scholastic achievement puts individuals at risk for poorer overall functioning in adulthood. Additionally, a CHR status is already associated with academic impairments compared to controls (Cornblatt et al., 2011), so the fact that the ADHD group was significantly more impaired than the CHR-only group indicates quite a severe level of impairment for those with CHR and ADHD. The consistent difference across development suggests that remediation efforts may not have been implemented and/or may not have been successful for those with ADHD. It also suggests that the ADHD and non-ADHD CHR groups could be differentiated at an early age based on their developmental trajectory.

The results also indicate that the ADHD group is not significantly impaired in social domains in comparison with the non-ADHD CHR group. This was unexpected since ADHD is typically associated with both poorer academic and social functioning (Barkley, 2002). CHR for psychosis is also associated with poorer social functioning, so it may be that while both groups are impaired in this domain compared to non-CHR controls, their social impairments are comparable to each other. Overall, it appears that in a CHR sample, an ADHD diagnosis is associated with additional impairment in scholastic, but not social domains.

Finally, the separate sex analysis revealed that while there is a main effect of ADHD on premorbid functioning in females, it is not significant in males. This may be due to sex differences in the diagnosis of ADHD and the resulting differences in severity of diagnosed ADHD. There is a large and well-documented gender gap in children presenting to health care professionals for help with ADHD symptoms (e.g., Quinn & Madhoo, 2014; Ohan & Visser, 2009). Males are diagnosed with ADHD much more frequently than females and this is probably due to many factors including implicit bias on the part of clinicians (Bruchmuller et al., 2012), a lack of understanding of ADHD symptoms in females (Ohan & Johnson, 2005), less disruptive behaviors in ADHD females (Gershon & Gershon, 2002), and potentially better coping skills and fewer overall impairments in females with ADHD (Biederman et al., 2002). Additionally, the referral and diagnosis biases against females may result in clinic-referred females with ADHD displaying overall more severe impairments than non-referred females with ADHD, and even more severe impairments than referred males with ADHD (Gaub & Carlson, 1997). It is essentially harder to females to meet the threshold for ADHD diagnosis. So when they do, the difference in impairment between ADHD and non-ADHD females may be greater than the difference in impairment between ADHD and non-ADHD males. This theory fits with our findings as both males and females with ADHD endorsed higher mean impairment ratings than their non-ADHD counterparts, but the difference was only large enough to meet be considered statistically significant among females.

Differences in Familial Risk for Psychosis and other Mental Illness

The results from the third analysis, displayed in Table 7., indicate that the ADHD and non-ADHD groups differed significantly in terms of their family history for psychological disorders. Separate sex analyses, displayed on Tables 8. and 9. and Figure 2., indicated that many

of these differences may be attributed to sex differences within groups. For the purposes of clarity, interpretations for each analysis are provided separately below.

Family History of Psychosis

Results from the initial regression analyses revealed that ADHD was a significant predictor of number of relatives with psychosis. The separate sex analyses revealed that whereas this effect held for females, for males, ADHD was not a significant predictor of family history of psychosis. Further, for males, ADHD was not even close to being considered a significant predictor (B=0.188, p=0.592), whereas for females ADHD appeared to predict number of relatives with psychosis quite strongly (B=1.907, p=0.000097). In fact, the results indicate that family members with psychosis are 6.7 times more likely in the females with ADHD compared to the females without ADHD. The different results for each sex are striking and indicate that the significant association of ADHD and relatives with psychosis observed in the initial regression was likely driven solely by the strong association within females.

The effect for females seems large, especially in comparison to the same analysis in males. One interpretation may be that for events of a very low base rate (such as having family members with psychosis), even a small, possibly chance-related increase in these events for one group may result in a strongly significant finding. This chance-related effect may be especially strong in a smaller group (e.g., females with 56 ADHD and 57 non-ADHD participants compared to 96 ADHD males and 100 non-ADHD males). While this possibility cannot be fully discarded, an examination of Figure 2., shows that the number of ADHD females reporting any family history of psychosis is double that of females without ADHD (20 vs. 9), which suggests that the ADHD effect within females was not solely due to one or two outliers who reported a very large number of family members with psychosis. Additionally, an examination of the

confidence intervals for both male and female analyses reveal that even though the confidence interval is larger for females (due to the smaller sample size), the male and female confidence intervals do not overlap, even at the high end of the male and the low end of the female confidence interval. This indicates that under most conditions of chance, the Exp(B) would still be higher for females than males. Overall, it appears unlikely that this result can be explained simply as a Type 1 error.

Assuming this result is valid, it indicates that the female ADHD-CHR participants have more of a 'genetic loading' for psychosis than non-ADHD females. In seeking to understand why this effect might exist for females but not males, one possible explanation centers on the idea that being female may typically be protective against ADHD and early onset of psychotic symptoms. Many studies have found males are more vulnerable to severe obstetric complications (Preti et al., 2000; O'Callaghan et al., 1992; Dalman et al., 1999), and other environmental risk factors for ADHD (Biederman et al., 2014), many of which are also risk factors for psychosis. As previously discussed, females with similar ADHD-related impairments are less likely to receive an ADHD diagnosis (Bruchmuller et al., 2012). Additionally, in the psychosis literature, female sex appears to be protective against early onset of psychotic symptoms, probably through the effects of estrogen (Rao & Kolsch, 2003). Later female age at onset is often cited as a major reason why psychosis and high risk samples are characterized by a majority of male participants, since most tend to recruit younger participants (Aleman et al., 2003). It follows then that females in this sample with both prodromal symptoms at a young age, and an ADHD diagnosis may represent an unusual group characterized by a greater 'inherent' vulnerabilities.

This theory fits with findings that increased familial loading in schizophrenia patients antagonizes the usual female protective effect such that women with a family history of

psychosis showed a younger age of onset and no difference from males in terms of age of first psychotic symptom (Konnecke et al., 2000). In relation to the present study it seems possible the entry requirements of CHR and ADHD comorbidity resulted in a sex-specific sampling effect such that, on average, females with ADHD have the stronger genetic disposition required to negate the generally protective female effect for both CHR and ADHD. This explanation also fits well with the familial subtype theory and suggests that for females, a high genetic load of psychosis confers a risk for neurodevelopmental deviance that may be expressed as ADHD at young ages, and as sub threshold psychotic symptoms during adolescence/young adulthood.

Family History of Mania

The analysis of family history of mania revealed that ADHD was a significant predictor of number of family members with mania. This is consistent with numerous previous findings that ADHD and bipolar disorder share a familial association (Faraone et al., 1997). This study extends these findings to a CHR group, indicating that an ADHD diagnosis is associated with an 80% increase in the chance of having family members with mania.

This association between ADHD and family history of mania was no longer significant when the analysis was repeated for the sexes separately. As can be seen in Table 9., both male and female ADHD groups were associated with a larger mean number of family members with psychosis than their non-ADHD counterparts, so the non-significant effect was likely due to the decrease in sample size in the separate sex analysis. In addition, mania, with only 62 total cases reported, was the least common disorder among family members of CHR participants. This smaller sample likely made any potential significant difference even harder to detect.

Family History of Depression

The analysis of family history of depression revealed that ADHD was a significant predictor of number of family members with depression. The separate sex analysis revealed that this effect remained significant for males only, and was not significant for females. In fact, in females, the ADHD group actually had a lower mean number of family members with depression than the non-ADHD group (although, not significant), indicating that the original overall significant effect of ADHD was due to the males in the sample.

ADHD is frequently associated with depression and the comorbidity between the two disorders is estimated at around 20 to 30% (Angold et al., 1999). Biederman (2005) proposed that ADHD and depression share common familial vulnerabilities and may be non-specifically associated (Biederman, 1991), whereas ADHD and bipolar disorder may instead be related through a specific familial subtype (Faraone et al., 2001; Wozniak et al., 1995). It is not easy to interpret why a relation between ADHD and family history of depression would be present only in males, and one explanation may be that this finding represents a Type 1 error. Alternatively, it may that the males represent a more typical ADHD sample and the increase in family history of depression in the male ADHD group is indicative of the non-specific familial vulnerabilities previously discussed. The female ADHD group, on the other hand, may represent quite a different type of ADHD sample due to the potential selection effect discussed previously, and as such, may be more representative of a specific ADHD-psychosis familial subtype that presumably is not as associated with depression.

Overall, it appears that ADHD is associated with an increase in family history for mental illness. In all cases the actual estimated means difference was very small between groups with and without ADHD. However, the significant effects suggest that there may be important etiological differences between groups. While the separate sex analyses were exploratory

analyses with smaller sample sizes, results strongly suggest that sex may also play an important role in the relationship between ADHD and psychosis.

Theories of ADHD-Psychosis Relation

Findings from this study have implications for several of the theories outlined previously. Firstly, no support was found for the severity continuum theory. While group differences in severity were observed in both prodromal symptoms and premorbid functioning, these differences were specific and not generalized across all domains. In fact, the ADHD and non-ADHD groups appeared remarkably similar in terms of severity of general and negative symptoms of psychosis, as well as in the domains of peer relations and sociability.

Partial support was found for the etiological/developmental subtype theory of ADHD-psychosis relations. In this study, ADHD was found to be associated with more severe disorganized symptoms of psychosis. As previously discussed, severity of disorganized symptoms is also associated with poorer outcome in psychosis. Additionally, more severe scholastic impairments were found to be associated with ADHD, which also bodes ill later general functioning outcomes in the ADHD group. These findings fit with the proposed characteristics of the etiological subtype as associated with poorer outcomes. However, there was no evidence in this study of more severe negative symptoms in the ADHD group. Further, the finding of stable premorbid differences between ADHD and non-ADHD groups across development suggests that groups may be identifiable at a young age, lending further support that ADHD may be associated with an etiological/developmental subtype of psychosis.

The theory of ADHD as a familial marker of psychosis can also be partially supported by findings from the current study. ADHD was found to be significantly associated with a family history of any mental illness; yet, it seemed to be most closely associated with a positive family

history specific for psychosis. Separate sex analyses revealed that this general ADHD effect was driven by a particularly strong female association between ADHD and family history of psychosis. It may be that in this CHR sample, the ADHD females are most representative of familial liability for neurodevelopmental impairment that can be expressed as both ADHD and psychosis. To the best of our knowledge, no theory of psychosis-ADHD relation directly incorporates any discussion of the potentially moderating effects of sex. So this exploratory finding is a unique contribution to this area of study.

Strengths and Limitations

There are several notable strengths of this study. Firstly, to date this is the largest collected sample of CHR youth. The large sample size enabled adequate power for detection of small effect sizes, even within analyses of smaller CHR subgroups. This was especially relevant for the exploratory separate sex analyses, which would not have been feasible with a smaller overall sample. Although this was a cross-sectional study of participants at their baseline evaluation, longitudinal data is also available which allows for follow-up analyses on related topics such as risk for conversion to psychosis for certain groups.

One major limitation of the study was the reliance on mostly self-reported diagnoses of ADHD. For many participants, their reported ADHD diagnosis could not be confirmed through medical records, and as such there may be concerns about the validity of the diagnosis. Future work can make use of additional data from neurocognitive tests to provide potentially more objective measures of impairment in ADHD-related domains such as attention and executive function. Additionally, despite the discussion of developmental time periods in the analysis of premorbid functioning, this study was cross-sectional in nature and thus limits conclusions about the direction of the association between ADHD and clinical correlates.

Conclusions

This investigation of psychosis-ADHD relations within a group of youth at clinical high risk for psychosis provides an optimal opportunity to learn more about a potential etiological subgroup of psychosis. Results from this study indicate that a clinical high risk for psychosis in combination with an ADHD diagnosis is associated with differences in prodromal symptom profile and premorbid functioning impairments, compared to CHR individuals without ADHD. Additional results from family history and exploratory analyses indicate that ADHD is associated with greater family history of psychosis in CHR females, whereas it is associated with greater family history of depression in CHR males. Overall, the findings from this study provide mixed support for the ADHD-psychosis subgroup theories, and highlight the need for additional investigations into the role of sex in ADHD-psychosis relations.

To our knowledge, this is the first study to investigate potential clinical correlates of ADHD within a clinical high risk group. It is also the first study to highlight the potentially moderating effect of sex in the association between ADHD and family history of psychosis and depression. The implications of the latter findings are unclear at this point, but it suggests that the etiology of the relation between ADHD and psychosis may be very different in males and females. In combination with recent findings that ADHD females are at significantly increased risk for conversion to psychosis (Dalsgaard et al., 2014; Dalteg et al., 2014), these findings also suggest that sex should not be ignored in future analyses on this topic.

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Table 1

Demographic Characteristics

Variable		ADHD (*n* = 163)	non-ADHD (*n* = 163)
Age (Mean ± SD)		17.55 ± 3.78	17.52 ± 3.77
Sex (*n*, %)	Male	103 (63.2%)	103 (63.2%)
	Female	60 (36.8%)	60 (36.8%)
Race (*n*, %)	Caucasian	108 (67.1%)	109 (67.3%)
	Black	24 (14.9%)	27 (16.7%)
	Asian	3 (1.9%)	3 (1.9%)
	Hispanic	3 (1.9%)	2 (1.24%)
	Native American	4 (2.5%)	8 (5.0%)
	Interracial	16 (10.0%)	16 (10.0%)
Antipsychotic Medication Status (*n*, %)	Baseline Use	27 (16.6%)	24 (14.7%)
	Lifetime Use	54 (33.1%)	37 (22.7%)
Stimulant Medication Status (*n*, %)	Baseline Use	31 (19.0%)	0 (0%)
	Lifetime Use	91 (55.8%)	0 (0%)

Table 2

Summary of Univariate Analyses of Prodromal Symptom Differences Between ADHD and non-ADHD groups

Symptom Domain	*df*	Mean Square	*F*	Significance	Group	Means	95% Confidence Interval	
							Lower Bound	Upper Bound
Positive	1	0.340	3.097	0.079	ADHD	2.482	2.429	2.534
					No ADHD	2.415	2.363	2.468
Negative	1	0.043	0.113	0.737	ADHD	2.363	2.264	2.461
					No ADHD	2.386	2.289	2.484
Disorganized (incl. D3)	1	6.489	18.86	p<0.001	ADHD	1.717	1.624	1.811
					No ADHD	1.427	1.334	1.52
General	1	0.004	0.014	0.905	ADHD	2.119	2.038	2.200
					No ADHD	2.112	2.032	2.192

Table 3

Summary of Univariate Analyses of Prodromal Symptom Differences Between the ADHD and non-ADHD group (excluding symptom D3)

Symptom Domain	*df*	Mean Square	*F*	Significance	Group	Means	95% Confidence Interval	
							Lower Bound	Upper Bound
Positive	1	0.298	3.185	0.075	ADHD	2.482	2.429	2.534
					No ADHD	2.415	2.363	2.468
Negative	1	0.181	0.543	0.462	ADHD	2.363	2.264	2.461
					No ADHD	2.386	2.289	2.484
Disorganized (excl. D3)	1	3.523	5.871	0.016	ADHD	0.908	0.789	1.028
					No ADHD	1.118	0.997	1.239
General	1	0.068	0.231	0.631	ADHD	2.119	2.038	2.200
					No ADHD	2.112	2.032	2.192

Table 4

Univariate Analyses of Prodromal Symptom Differences Between ADHD and non-ADHD groups, Separated by Sex

Sex	Symptom Domain	df error	Mean Square	F	Significance	Group	Mean
Male	Positive	191	0.616	5.021	0.026	ADHD	2.5133
						No ADHD	2.4004
	Negative	191	0.059	0.156	0.693	ADHD	2.3975
						No ADHD	2.4324
	Disorganized	191	2.933	8.104	0.005	ADHD	1.7226
						No ADHD	1.4760
	General	191	0.034	0.136	0.713	ADHD	2.1061
						No ADHD	2.1327
Female	Positive	113	0.004	0.046	0.831	ADHD	2.4284
						No ADHD	2.4401
	Negative	113	0.001	0.002	0.965	ADHD	2.3038
						No ADHD	2.3089
	Disorganized	113	3.797	12.075	0.001	ADHD	1.7085
						No ADHD	1.3451
	General	113	0.114	0.419	0.519	ADHD	2.1411
						No ADHD	2.0781

Males: ADHD N=102, non-ADHD N=100

Females: ADHD N=59, non-ADHD N=60

Table 5

Mixed Design ANOVA Effects on Premorbid Functioning

Main Effects	F	*df*	*df* error	Significance
Developmental Period	12.94	2.00	404.00	p<0.001
Domain of Function	42.81	2.00	404.00	p<0.001
ADHD Status	4.31	2.00	202.00	0.039
Interaction Effects				
Developmental Period x ADHD Status	0.46	1.88	378.98	0.618
Domain of Function x ADHD Status	6.17	1.76	354.53	0.004
Developmental Period x Domain of Function	16.29	3.27	660.56	p<0.001
Developmental Period x Domain of Function x ADHD Status	1.83	3.27	660.56	0.135

Table 6

Mixed Design ANOVA Effects on Premorbid Functioning - Separate Sex Analyses

	Main Effects	F	*df*	*df* error	Significance
Males	Developmental Period	13.42	1.85	252.16	p<0.001
	Domain of Function	37.89	1.78	242.09	p<0.001
	ADHD Status	1.02	1.00	136.00	0.314
	Interaction Effects				
	Developmental Period x ADHD Status	0.08	1.85	252.16	0.909
	Domain of Function x ADHD Status	3.34	1.78	242.09	0.043
	Developmental Period x Domain of Function	10.73	3.13	426.30	p<0.001
	Developmental Period x Domain of Function X ADHD Status	1.61	3.13	426.30	0.183
	Main Effects	F	*df*	*df* error	Significance
Females	Developmental Period	3.75	1.83	117.25	0.030
	Domain of Function	10.32	1.70	108.56	p<0.001
	ADHD Status	4.69	1.00	64.00	0.034
	Interaction Effects				
	Developmental Period x ADHD Status	1.05	1.83	117.25	0.348
	Domain of Function x ADHD Status	4.06	1.70	108.56	0.026
	Developmental Period x Domain of Function	6.30	3.37	216.00	p<0.001
	Developmental Period x Domain of Function x ADHD Status	0.53	3.37	216.00	0.683

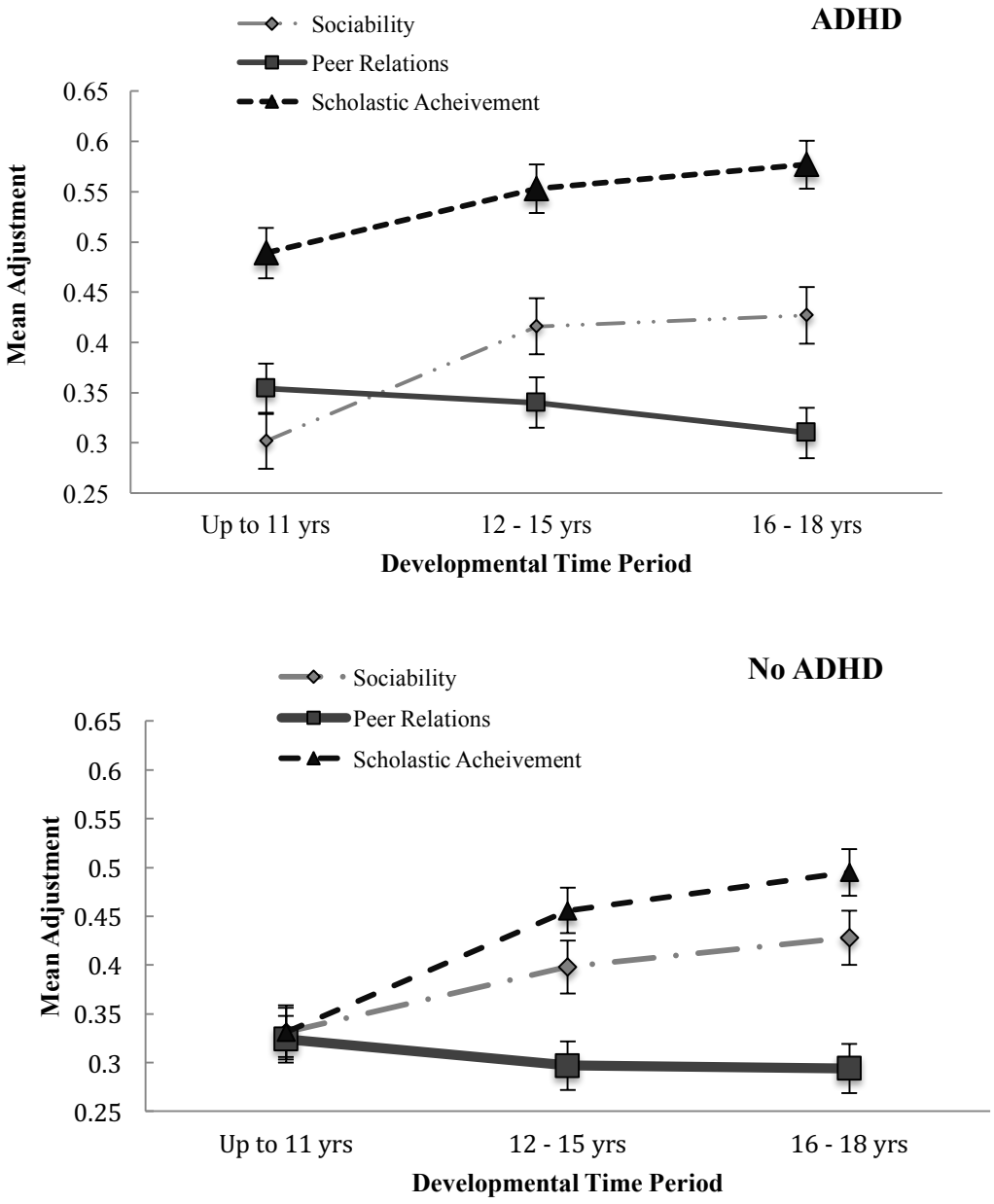


Figure 1

Graph showing Domain of Functioning X Developmental Time Period Interaction for ADHD and non-ADHD groups

Table 7

Negative Binomial Regression Analyses for ADHD as a Predictor of Family History of Mental Illness

Outcome variable	B	Std. Error	Wald Chi-Square	*df*	Significance	Exp(B)	95% Wald Confidence Interval for Exp(B)	
							Lower	Upper
Psychosis (# relatives)	0.814	0.2795	8.477	1	0.004	2.256	1.305	3.902
Mania (# relatives)	0.601	0.2972	4.096	1	0.043	1.825	1.019	3.267
Depression (# relatives)	0.412	0.2029	4.117	1	0.042	1.509	1.014	2.247

All analyses were ADHD vs. non-ADHD

Table 8

Separate Sex Regression Analyses for ADHD as a Predictor of Family History of Mental Illness

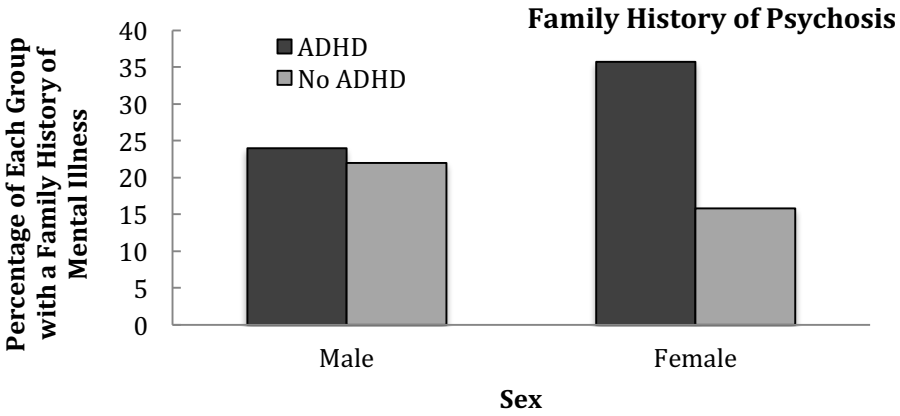
Outcome Variable	Group	B	Std. Error	Wald Chi-Square	*df*	Significance	Exp(B)	95% Wald Confidence Interval for Exp(B)	
								Lower	Upper
Psychosis (# relatives)	Male	0.188	0.3512	0.287	1	0.592	1.207	0.606	2.402
	Female	1.907	0.4891	15.201	1	p<0.001	6.731	2.581	17.554
Mania (# relatives)	Male	0.517	0.3663	1.991	1	0.158	1.677	0.818	3.438
	Female	0.756	0.5065	2.229	1	0.135	2.13	0.789	5.749
Depression (# relatives)	Male	0.721	0.2606	7.666	1	0.006	2.057	1.235	3.428
	Female	-0.061	0.3317	0.034	1	0.854	0.941	0.491	1.802

All analyses were ADHD vs. non-ADHD

Table 9

Estimated Marginal Mean Number of Family Members with Mental Illness by Group

Sex	Number of Family Members with Psychosis		Number of Family Members with Mania		Number of Family Members with Depression	
	ADHD	non-ADHD	ADHD	non-ADHD	ADHD	non-ADHD
Combined	0.012	0.005	0.009	0.005	0.028	0.019
Male	0.009	0.008	0.009	0.005	0.030	0.015
Female	0.018	0.003	0.009	0.004	0.025	0.025



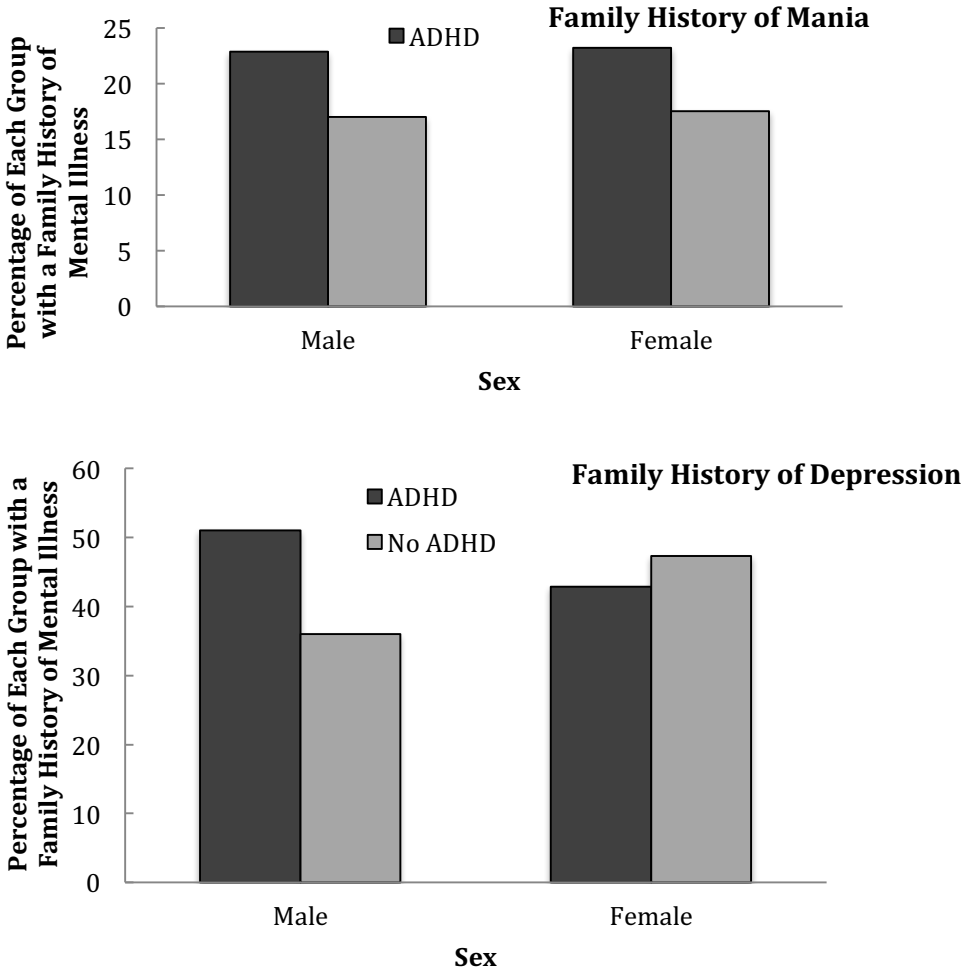


Figure 2

Graphs Showing Percentage of Each Group with a Family History of Mental Illness, Separated by Sex