Family history of psychosis, social risk factors and the psychosis risk syndrome

by

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Abstract

The goal of this thesis was to determine whether individuals with a family history of psychosis who met established criteria for being at risk of developing a psychotic disorder, i.e. met criteria for a psychosis risk syndrome (FHR-COPS), differed in terms of social risk factors from individuals with a family history of psychosis who did not meet criteria for a psychosis risk syndrome (FHR-Non). Results were that FHR-COPS individuals began smoking cannabis at an earlier age, had a lower IQ, and evidenced more anxiety, increased negative schemas about the self and poorer functioning. Onset of cannabis use at an earlier age was the one significant factor that determined belonging to the FHR-COPS group. These preliminary results are promising in determining potential risk factors for the development of psychosis in those who are already at risk for psychosis on the basis of a family history.
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<th>Full Form</th>
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<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
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<tr>
<td>APS</td>
<td>Attenuated Positive Symptoms</td>
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<tr>
<td>BCSS</td>
<td>Brief Core Schema Scale</td>
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<td>BIPS</td>
<td>Brief Intermittent Psychotic Symptoms</td>
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<tr>
<td>CAARMS</td>
<td>Comprehensive Assessment of the At-Risk Mental States</td>
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<tr>
<td>CDSS</td>
<td>Calgary Depression Scale for Schizophrenia</td>
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<td>CHR</td>
<td>Clinical High Risk</td>
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<tr>
<td>COMT</td>
<td>Catecho-O-Methyltransferase Gene</td>
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<tr>
<td>COPS</td>
<td>Criteria of Psychosis-risk Syndromes</td>
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<td>EHRS</td>
<td>Edinburgh High Risk Study</td>
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<tr>
<td>FHR</td>
<td>Family High Risk</td>
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<td>FHR-COPS</td>
<td>Family High Risk plus Psychosis Risk Syndrome</td>
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<td>FHR-Non</td>
<td>Family High Risk and no Psychosis Risk Syndrome</td>
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<td>FIGS</td>
<td>Family Interview for Genetic Studies</td>
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<td>GAF</td>
<td>Global Assessment of Functioning</td>
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<tr>
<td>GF:R</td>
<td>Global Functioning: Role</td>
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<tr>
<td>GF:S</td>
<td>Global Functioning: Social</td>
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<tr>
<td>GRD</td>
<td>Genetic Risk and Deterioration</td>
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<td>IQ</td>
<td>Intelligence Quotient</td>
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<tr>
<td>NAPLS</td>
<td>North American Prodrome Longitudinal Study</td>
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<tr>
<td>PAS</td>
<td>Cannon-Spoor Premorbid Adjustment Scale</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>SAS</td>
<td>Social Anxiety Scale</td>
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<tr>
<td>SCID</td>
<td>Structured Clinical Interview for DSM-IV Disorders</td>
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<td>SES</td>
<td>Socioeconomic Status</td>
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<td>SIAS</td>
<td>Social Interaction Anxiety Scale</td>
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<tr>
<td>SIPS</td>
<td>Structured Interview for Prodromal Syndromes</td>
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<td>SOPS</td>
<td>Scale of Prodromal Symptoms</td>
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<td>TBI</td>
<td>Traumatic Brain Injury</td>
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<td>WASI</td>
<td>Wechsler Abbreviated Scale for Intelligence</td>
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Chapter One: Introduction

In schizophrenia research, there is increasing interest in detecting individuals in the early stages or prodromal phase of the illness. The motivation for this is largely because of the chronic nature of schizophrenia, and the devastating impact it can have on the individual affected, their families, and society as a whole. While treatments have improved over the years, there are still a large proportion of those with schizophrenia who struggle with their symptoms and suffer in their ability to work, attend to self-care, and maintain and keep relationships (McGlashan et al., 2010). Therefore, attempts to understand the development of schizophrenia and its early stages will not only lead to an improved understanding of psychosis but potentially help us to find appropriate intervention and prevention strategies for the future.

The word ‘prodrome’ describes the ‘forerunner of an event’ (McGlashan et al., 2010). In schizophrenia, the prodromal phase therefore refers to the signs and symptoms that a person experiences prior to the onset of a full blown syndrome (Yung et al., 2004). Recent research developments led to the potential to identify the putatively prodromal. Reliable criteria have been developed to identify individuals who may be at risk of developing psychosis and thus experiencing a potential prodrome for psychosis (McGlashan, 2008). The criteria for meeting an at risk mental state was first introduced by Alison Yung and colleagues in Melbourne (Yung and McGorry, 1996) and incorporated into the Comprehensive Assessment of the At-Risk Mental States (CAARMS). These criteria were modified by McGlashan and colleagues (McGlashan et al., 2010) to form the Criteria of Psychosis-risk Syndromes (COPS). The COPS are evaluated using the Structured Interview for Prodromal Syndromes (SIPS) and the Scale of Prodromal Symptoms
(SOPS). In a recent review, it was shown that both measures demonstrate excellent reliability and predictive validity (Addington and Heinssen, 2011).

Both the Melbourne criteria and the COPS have three possible prodromal syndromes - attenuated positive symptoms syndrome (APS), genetic risk and deterioration syndrome (GRD) and/or brief intermittent psychotic symptoms syndrome (BIPS). APS requires the presence of at least one particular positive psychotic symptom (unusual thought content, suspiciousness, grandiose ideas, perceptual abnormalities, or disorganized communication) of insufficient severity to meet diagnostic criteria for a psychotic disorder. The GRD requires having a combination of both functional decline and genetic risk; genetic risk refers to having either schizotypal personality disorder or a first-degree relative with a schizophrenia spectrum disorder (McGlashan et al., 2010). The BIPS state requires the presence of any one or more threshold positive psychotic symptoms (unusual thought content, suspiciousness, grandiosity, perceptual abnormalities, and disorganized communication) that are too brief to meet diagnostic criteria for psychosis. Researchers are therefore able to prospectively follow the course of the illness with the goal of being able to distinguish between early on differences for those who go on to develop schizophrenia from those who do not. Current evidence indicates that approximately 35% of these at risk individuals will go on to develop a full blown illness within 2 years (Cannon et al., 2008). Since this risk is determined on the basis of clinical symptoms these individuals are considered to be at clinical high risk (CHR) of developing psychosis.
Besides being at CHR for psychosis, an individual’s risk can also be determined based solely on having a family history. The risk is defined by the relationship to an affected individual, usually a first degree relative and usually a parent. The risk here for developing schizophrenia is approximately 10% compared to 1% in the general population, and this risk increases with the degree of the genetic relationship (de la Serna et al., 2011). These individuals have been referred to in the literature as genetic high risk or more correctly family high risk (FHR) individuals.

There have been several studies in the literature which have studied FHR individuals longitudinally. Some of these studies follow subjects from birth (Fish, 1960; Marcus et al., 1985); some from late childhood as in the New York High Risk Study and Israeli High Risk Study (Erlenmeyer-Kimling and Cornblatt, 1992; Erlenmeyer-Kimling, 2000; Nagler and Mirsky, 1985; Nagler, 1985) and some from adolescence (Cannon and Mednick, 1993; Johnstone et al., 2002a; Lawrie et al., 2008; Mednick et al., 1987). These FHR studies have shown that approximately 25-60% of high risk children evidenced some or all of the following when compared to non high risk children; poorer timing of developmental milestones, poorer cognition, poorer social functioning and more soft neurological signs (Cannon et al., 2003). There is also evidence from these studies that psychopathology may also play an important role. For example, the New York High Risk Study found that behavioural problems predicted the later development of schizophrenia while the Copenhagen High Risk Study (Mednick et al., 1987) found that those who went on to develop schizophrenia were more likely to be rated by their teachers as disruptive, nervous, lonely and anxious. At the latest follow up for this study the authors found
that in addition to meeting criteria for a psychotic disorder, 40% of the high risk individuals also fulfilled criteria for a comorbid diagnosis of an Axis I or II disorder.

One of the more recent FHR studies is the Edinburgh High Risk Study (EHRS) which differed from the earlier studies. Recruitment included subjects with two family members with a diagnosis of schizophrenia and had a focus on neuroimaging and neuropsychology not previously available in the earlier FHR studies. This study did not find the soft sign differences previously reported or general IQ differences but did observe differences in executive function and memory. In terms of brain structure, the FHR sample had smaller right and left prefrontal lobes, and right and left thalami when compared to healthy controls (Miller et al., 2002; Johnstone et al., 2002b; Johnstone et al., 2005; Johnstone et al., 2000). While there are some advantages of these FHR studies, such as the power of prospective data, standard assessments, specific controls and true blindness as to outcome, there are disadvantages as well. For instance these types of studies take a long time with both participant and investigator dropout. Recruitment is hard and what once may have been state of the art tools easily become outdated.

It has been suggested that there is an interaction between the child-rearing environment and genetic risk and the later development of schizophrenia (Mirsky et al., 1985; Cannon and Mednick, 1993) and more recently research has begun to consider environmental risk with a focus on the impact that environmental exposures might have. The role of certain biological and psychosocial risk factors such as urban upbringing, migration, low
IQ, childhood trauma and abuse, early cannabis use, and adverse childhood development at certain points in the lifespan have all been linked to the later development of psychosis.

1.1 Social Risk Factors & Psychosis

1.1.1 Urbanicity

There is evidence that those raised in an urban environment are at greater risk for developing schizophrenia and other psychoses (Pedersen and Mortensen, 2001; Pedersen and Mortensen, 2006; Kelly et al., 2010). A series of Danish cohort studies demonstrated evidence of a dose response relationship between urbanicity during upbringing and schizophrenia risk; that is, the risk of schizophrenia increased when individuals moved to a higher degree of urbanization during upbringing and vice versa. Additionally, the authors found that urbanicity at birth was explained by urbanicity at upbringing suggesting that it is likely the repeated circumstances that frequently occur in urban environments, such as infections, diet and exposure to pollutants, that are possibly the factors which were responsible for the association between urbanization and risk of schizophrenia (Pedersen and Mortensen, 2001; Pedersen and Mortensen, 2006). In addition to these factors, it has also been shown that the degree to which mutual trust and safety in neighbourhoods is perceived by children could have a developmental impact on their mental health (Krabbendam and van Os, 2005). A comprehensive meta-analysis (Krabbendam and van Os, 2005) suggested that approximately one third of all incidences of schizophrenia may be related to unknown but likely unconfounded environmental factors operating in the urban environment that may impact on the development of children and
adolescents to increase the later expression of psychosis-like symptoms, “at-risk mental states” and overt psychosis. This is not perceived to be phenotypically silent, because the rate of “at-risk mental states” characterized by subtle psychosis-like phenomena is also higher in urban areas. In addition to this the researchers found the risk of developing schizophrenia or other psychoses further increased when there was a family history of psychosis. It was predicted that approximately 20-35% of those exposed to both an urban environment, and a family history of psychosis had developed schizophrenia because of the synergistic action of the two factors (van Os et al., 2004). A very recent study investigated various environmental risk factors in a group of individuals considered to be at ultra-high risk for developing psychosis and found that urbanicity was a significant predictor for developing psychosis in this group (Dragt et al., 2011).

1.1.2 Migration

It has been shown that the prevalence of psychotic symptoms is greater among ethnic minorities, even after SES and cultural factors are accounted for (King et al., 2005). A recently published large incidence study found that younger age at the time of migration predicted psychotic disorders among immigrants in the Netherlands. More specifically, individuals who migrated between the ages of 0 and 4 had the most elevated risk for psychotic disorders, and this risk decreased with age (Veling et al., 2011). While there have been attempts to better understand this relationship, it appears to be quite complex which has led certain researchers to suggest that it is likely not only one factor that contributes to this association (Fearon and Morgan, 2006). One theory suggests that rates of psychosis are higher among individuals who
have migrated because there are possibly higher rates of psychosis to begin with from the county of origin. This theory was tested among a group of individuals who immigrated from Surinam to the Netherlands. However, despite higher rates of schizophrenia among these individuals in the Netherlands, this was not the case for rates in Surinam (Selten et al., 2005). It was therefore suggested that the increased rates in the Netherlands among Surinamese immigrants are more likely due to factors contributing to the transition of moving to a competitive Dutch society, rather than something characteristic of the Surinamese people. It therefore seems more reasonable to suggest that the association is more likely due to the social experiences that immigrant groups encounter. Interestingly it was found that among immigrant groups in the Netherlands, the incidence of psychosis was significantly higher in areas where the ethnic density of the neighbourhood was low, and that in areas where the ethnic density was high, the levels of psychosis were much more comparable to the levels in the general population (Veling et al., 2008). Thus it might be the aspects shared by immigrants that are more important than any specific background, and that being exposed to social defeat is a likely contributor (Cantor-Graae and Selten, 2005). A meta-analysis (Cantor-Graae and Selten, 2005) on migration demonstrated that a personal or family history of migration is an important risk factor for schizophrenia with greater effect sizes for those from developing versus developed countries and for second versus first generation immigrants. Further studies have suggested up to a fourfold increase in risk when migration history acts synergistically with other variables such as family dysfunction, suggesting that family dysfunction might be acting as a psychosocial stressor for vulnerable individuals (Patino et al., 2005). A recent review of the epidemiological
literature concluded with three key issues related to migration and psychosis; 1) the incidence of psychotic disorders is increased in most but not all immigrant groups around the world, 2) the degree to which the rates are increased will vary according to ethnic group and country, and 3) the increased risk pertains to second-degree immigrants, and possibly later generations (Veling and Susser, 2011). This latter finding was further confirmed by a recent meta-analysis which shows that increased schizophrenia and other related disorders affects not only first generation immigrants, but also second generation immigrants, indicating strong evidence that post migration factors may be equally or even more important than pre-migration factors (Bourque et al., 2011).

Interestingly, additional evidence suggests that it is perceived discrimination, regardless of ethnic group, and not necessarily actual discrimination that is associated with psychotic illness. The hypothesis was based on the idea that a chronic experience of discrimination would lead to a paranoid attributional belief system, and therefore an increased rate of psychotic like experiences. Even after controlling for different confounds such as depressive symptoms, low self-esteem, and neuroticism, the authors found that perceived discrimination predicted the incidence of delusional ideation in a dose-response fashion (Janssen et al., 2003). Similar results were also displayed in another study which showed that both the interpersonal experience of racism, and perception of racism each have independent effects on the risk for psychosis, regardless of the ethnic group an individual belongs to (Karlsen et al., 2005).
1.1.3 Low IQ

It has been suggested that low IQ may be a risk factor for developing psychosis. In one of the studies linking assessments from the Israeli draft board with data on schizophrenia from the Israeli Psychiatric Registry, Reichenberg and colleagues (Reichenberg et al., 2005; Reichenberg et al., 2006) reported that low premorbid IQ did appear to be a risk factor in that 28% of individuals that later developed schizophrenia displayed clinically significant intellectual impairments. They also reported that throughout development, children who have lower than expected IQ scores were shown to be at an increased risk of developing schizophrenia. Interestingly, this was not the case for any other disorder investigated, suggesting that intellectual deterioration might be associated with an increased risk of developing schizophrenia specifically (Reichenberg et al., 2005). In a separate study by the same researchers (Reichenberg et al., 2006) it was found that while those that developed schizophrenia maintained an average general IQ, variability in intra-individual intellectual performance was a significant risk factor. Individuals with the highest variability were 3.8 times more likely to have schizophrenia later in life. In a further study from the same group, Weiser and colleagues (Weiser et al., 2007) looked at the impact that learning disorders had on those with average IQ that later went on to develop schizophrenia. When comparing the impact of both impaired reading comprehension and mathematical ability, it was found that those with impaired reading comprehension were at an increased risk for later hospitalization of schizophrenia. Those who had both impairments were more likely to have current or future psychopathology. A recent systematic review assessing current evidence for non-genetic risk
factors of schizophrenia found that low IQ was among one of the strongest antecedents of schizophrenia (Matheson et al., 2011). However it should also be noted that other studies have failed to find a predictive relationship between intellectual functioning and later psychosis (Carter et al., 2010) indicating some contradictions in the literature.

1.1.4 Trauma

Several lines of evidence suggest a possible association between a history of trauma in childhood and later psychosis or the presence of psychotic like experiences (Shevlin et al., 2006; Read et al., 2005; Janssen et al., 2005; Spauwen et al., 2006; Janssen et al., 2004; Husted et al., 2012). In a preliminary study, Bechdolf and colleagues (Bechdolf et al., 2010) attempted to determine whether trauma predicts conversion to psychosis in an ultra-high risk group. They found that approximately 70% had experienced at least one type of trauma, and that the rates of conversion to psychosis significantly increased when the type of trauma was sexual abuse. Kelleher and colleagues (Kelleher et al., 2008) also found that among a sample of adolescents, those who reported psychotic symptoms were six times more likely to have experienced physical abuse, and ten times more likely to have witnessed domestic violence. The investigators also looked at the impact that bullying might have on psychosis and were specifically interested in whether the outcome of psychosis would be dependent on whether an individual was more likely to be a victim of bullying, perpetrator of bullying, or both a bully and a victim. Interestingly, while it was demonstrated that those who reported psychotic symptoms were significantly more likely to be identified as a ‘bully’, the vast majority of this group also
reported being a victim of bullying; a characteristic not typical of a bully profile and therefore perhaps possibly unique to the relationship to psychosis. A more recent study found that after controlling for SES, low IQ, early psychopathology, and genetic susceptibility, maltreatment by an adult and bullying by peers were significantly associated with children’s report of psychotic symptoms (Arseneault et al., 2011). Another recent study has shown that total childhood trauma was significantly associated with psychosis in a dose response fashion indicating that the rates of reported trauma were highest for individuals with psychosis. In addition to this, the siblings of these patients also evidenced more trauma compared to healthy controls (Heins et al., 2011). Interestingly it has also been shown that both trauma experienced early and late in life are highly correlated and that they work additively to increase the risk of psychosis (Lataster et al., 2011).

As much of the trauma literature appears to focus on more severe overt forms of trauma, a review by Read and colleagues (Read et al., 2005) addressed the possibility that less severe but chronic and persistent forms of trauma might be just as detrimental. Interestingly, it was evident that subtle, ongoing childhood difficulties seem to be just as related to psychosis as an overt act of abuse. Other research in the trauma literature has investigated whether or not there are associations between trauma and the development of specific symptoms of psychosis. For example, an internet study (Gracie et al., 2007) assessed whether there were specific psychological mechanisms by which trauma might influence a predisposition to hallucinations and paranoia. They found that negative beliefs about self and others were most
strongly associated with a predisposition to paranoia, and therefore suggested that negative schematic beliefs might be a mediator between the relationship of trauma and paranoia.

While research in the area of trauma and psychosis is growing, there are still several methodological issues that should be addressed before definite conclusions can be drawn. A recent critical review (Bendall et al., 2007) of the literature linking childhood trauma with the later onset of psychotic or psychotic like experiences listed some of these concerns. The review stated that most of the studies in this area lack a comparison to any control group, and most have low power. In addition to this, the attention to mediating factors is typically not addressed and the measurement of childhood trauma is inconsistent. There is also a need for more longitudinal assessment of these concerns as the majority of the research looked at in the review is cross sectional.

1.1.5 Cannabis Use

The popular question of debate on cannabis use and psychosis is whether cannabis use may cause psychosis or whether the use of cannabis is a result of having a psychotic illness. Several meta-analyses (Arseneault et al., 2004; Henquet et al., 2005b) present a range of evidence that the use of cannabis does increase the risk of later developing a psychotic illness. Even when the authors of these reviews adjust for variables such as age, sex, social class, ethnicity, other drug use, and urbanicity the effect of cannabis on the later development of a psychotic illness remains significant. Cannabis use has been associated with an earlier onset of schizophrenia, as well as relapse in cannabis using male patients compared to non-cannabis
using male patients (van Dijk et al., 2012). However, what is most important to note is that only a small proportion of cannabis users actually develop psychosis. There are several possible explanations for this. First, this may be a dose response effect; that is, it can be partially explained by the amount and duration of use. This has been supported by several studies (Henquet et al., 2005a). Another possibility is the age at which an individual uses cannabis. Adolescence seems to be a particularly risky time. For example, results of the Dunedin Birth Cohort Study in New Zealand suggested that the use of cannabis before age 15 was associated with a greater risk of developing schizophreniform disorder by age 26 (Arseneault et al., 2002). This has been supported by other quality studies in Greece (Stefanis et al., 2004) and Trinidad (Konings et al., 2008). Thirdly, it is possible that only a minority of cannabis users develop psychosis because they are genetically vulnerable.

The issue of gene-environment interplay has been reviewed in detail in a recent comprehensive review (Henquet et al., 2008). These authors suggest that genetic vulnerability to cannabis abuse seems to be polygenic and possibly mediated by an early response to cannabis use. There is no support for the notion that genetic influences on cannabis use are associated with being vulnerable or prone to psychosis. However, there is much support for a genetic-environment interplay underlying what can be considered to be a complex interaction between cannabis use and psychosis. In their comprehensive review, Henquet and colleagues (Henquet et al., 2008) present evidence that those who developed psychosis after cannabis use were more likely to have a positive family history of schizophrenia. Secondly, they reviewed in detail the work of Caspi and colleagues (Caspi et al., 2005) who were the first to demonstrate
direct evidence of gene-environment interplay in the cannabis-psychosis relationship by studying a functional polymorphism in the catecho-O-methyltransferase (COMT) gene.

Another potential interaction is between stress and cannabis use. Henquet and colleagues present (Henquet et al., 2008) evidence that the additive effects of early childhood trauma and cannabis use on the later development of psychosis may result from a cross-sensitization process between repeated exposures to various stressful events plus the use of cannabis.

In summary there appears to be sound evidence that cannabis use may contribute to the development of psychosis. However, this is only the case for a very small proportion of those who use cannabis.

1.1.6 Traumatic Brain Injury

Traumatic brain injury (TBI) has been linked with several adverse mental health outcomes, with its role as a risk factor for schizophrenia being a contested topic in the literature (Molloy et al., 2011). One recent systematic review found that there is little evidence of an association between head injury and psychosis (Hesdorffer et al., 2009) while another more recent meta-analysis found an increased risk of schizophrenia following TBI of about 60%. While much of the criticism in this area points to the issue that there is a lack of critical and systematic reviews available (David & Prince, 2005), what does appear to be more consistent is the relationship between the interaction of a family history of psychosis and TBI as a risk factor for psychosis (Kim, 2009). One example of this comes from a case-control study that looked at
childhood TBI among a group of individuals with schizophrenia and their unaffected siblings. The results of their study concluded that childhood TBI was significantly associated with schizophrenia and therefore suggested that the relationship of TBI to schizophrenia represents a combination of a pre-existing genetic vulnerability and an environmental insult to the brain (AbdelMalik et al., 2003). Similarly, Malaspina and colleagues (Malaspina et al., 2001) also found that TBI doubled the risk of schizophrenia among individuals that had at least two first-degree relatives with psychosis, while this same result was not found among affected individuals without a family history of psychosis. The authors therefore suggested that TBI works synergistically with genetic predisposition and risk for schizophrenia.

In conclusion, while it is difficult to fully understand the relationship between TBI and schizophrenia due to methodological issues and the lack of rigorous studies on the topic, there does appear to be evidence to support the investigation of TBI among individuals with a family history of psychosis.

1.1.7 Summary of Social Risk Factors

The impact that individual risk factors have on the development of psychosis has been discussed at length. Evidence that migration, urbanicity, low IQ, trauma, cannabis use and traumatic brain injury individually have a significant influence on the development of psychosis has been reviewed. There is also some evidence that many of these factors are working in combination with one another (van Os et al., 2004), or additively to even further increase risk of developing psychosis. A recent study by Harley and colleagues (Harley et al., 2009) found that
while cannabis use and trauma were significantly associated with the risk of experiencing psychotic symptoms, this risk significantly increased with the additive interaction between the two. Another study also found evidence that cannabis use, trauma and urbanicity had an additive effect and that accumulation of these factors at baseline contributed to the later persistence of psychosis (Cougnard et al., 2007). A more recent study has revealed a significant interaction between cannabis use and urbanicity and found that the effect of cannabis use on psychotic symptoms was much stronger for individuals who grew up in an urban environment. This relationship remained after controlling for confounding factors such as age, sex, SES, and other drug use (Kuepper et al., 2011). There has also been evidence that the interaction of early cannabis use and sexual trauma was a significant predictor for determining the outcome of psychosis (Houston et al., 2008), a finding which has recently been replicated (Konings et al., 2012). These types of interactions have also been displayed in family high risk studies, indicating that cannabis use may synergistically combine with pre-existing psychosis liability to cause positive and negative symptoms of psychosis (Genetic Risk and Outcome in Psychosis (GROUP) Investigators, 2011). These findings, along with the individual social risk factors previously discussed, suggest that the likelihood of developing psychotic symptoms becomes greater as the number of risk factors that an individual is exposed to increases.

The early FHR studies provided a basis for research in the area of psychosis showing that risk of developing schizophrenia increases from 1% to 10% when an individual has a first degree relative affected by the illness. Research then took a shift away from FHR design to determine those who were at clinical high risk on the basis of the presence of attenuated positive
symptoms, which is a large focus of the research today. It is possible that in the earlier FHR studies participants may or may not have evidenced attenuated or subthreshold psychotic symptoms as this was not an area under study at the time. Of course, many of the participants who meet clinical high risk criteria are also at family high risk, either because they have developed attenuated psychotic symptoms or have developed a recent decline in functioning and meet the Genetic Risk and Deterioration Syndrome. This raises the question of what factors contribute to the development of the psychotic risk syndrome in those with FHR. There is evidence for the individual and additive impact of social risk factors on the development of psychosis and that there is some synergy between FHR environmental exposures with respect to the development of psychotic like experiences as well as psychosis (van Os et al., 2008). Therefore it is possible that certain risk factors do play a role in the development of psychosis but only in combination with one another and in particular for those who are at family high risk (FHR) of psychosis.

1.2 Aims and Hypothesis of the Current Study

The overall aim of this project was to determine the differences between individuals with FHR who meet a psychosis risk syndrome and FHR individuals who do not in terms of social risk factors. The primary hypothesis is that the FHR group with a psychosis risk syndrome will evidence more social risk factors defined as previous traumatic experiences, greater sense of discrimination, ever having had a head injury, cannabis use before age 15 and lower IQ compared to non-psychosis risk syndrome FHR individuals and to healthy controls. Urbanicity
was not assessed as the sample population all reside within the city of Calgary and there is a lack of urban diversity. The secondary hypothesis is that in terms of functioning and psychopathology the non-psychosis risk syndrome FHR group will occupy an intermediate position relative to the psychosis risk syndrome FHR group and healthy controls.
Chapter Two: Methods

2.1 Participants

The sample consists of 25 participants with a family high risk of psychosis who meet criteria for having a psychosis risk syndrome (FHR-COPS); 25 participants who have a first degree relative with a psychotic disorder that do not meet COPS criteria (FHR-Non) and 25 healthy controls with neither a family history of psychosis or evidence of clinical high risk symptoms. The FHR sample had either a mother (n=17, 36%) or father (n=15, 33%) with psychosis. The remainder of participants had either a brother (n=13, 26%), or sister (n=4, 8%) with psychosis, and only one participant had both a mother and sister with psychosis (n=1, 2%). The FHR-COPS group and the healthy controls were recruited as part of the ongoing NIMH funded North American Prodrome Longitudinal Study 2 (NAPLS 2). The NAPLS project was established to investigate predictors and mechanisms of conversion to psychosis (Addington et al., submitted). Sample size was chosen based on NAPLS current recruitment numbers of family high risk individuals. Recruitment of individuals at clinical high risk for psychosis is difficult with most research projects recruiting between 20 and 35 participants per year. Those with a family history are a subgroup of this population and represent approximately 18% of these individuals. Therefore, over a period of 48 months it was possible to recruit 25 FHR-COPS. This number was matched with 25 FHR-Non individuals and 25 healthy controls. Since there was neither preliminary data nor past literature on which to determine adequate sample size, this study will serve as preliminary data to develop appropriate sample sizes for future studies.
The FHR participants without symptoms were recruited from a variety of sources. Notices were posted in mental health clinics particularly those with schizophrenia programs, as well as in community settings. Mass emails were sent out to various departments throughout the university informing potential participants about the research. The Schizophrenia Society of Alberta was approached and presentations were done at their monthly meetings.

All eligible and interested participants had the study explained to them orally by a clinician, read the full consent document, and were provided with informed consent (consent was obtained from parents/guardians in the case of minors). Confidentiality was maintained by assigning a study number to each participant and subsequently coding all collected data accordingly. Information was protected either by password in the case of electronic storage or by a locked filing cabinet in the case of hard copies.

2.2 Inclusion and Exclusion Criteria

2.2.1 FHR-COPS group

Inclusion Criteria

1. Male or female between 12 and 35 years old.
2. Understand and sign an informed consent (or assent for minors) document in English.
3. Must have a first degree relative with a psychotic disorder.
4. Must meet diagnostic criteria for a psychosis risk syndrome as per COPS Criteria or if under 19 meet criteria for schizotypal personality disorder.
Exclusion Criteria

1. Must not meet criteria for current or lifetime Axis I psychotic disorder, including affective psychoses and psychosis NOS.

2. Impaired intellectual functioning (i.e IQ<70); however those with an IQ in the 65-69 range were included if the WRAT reading >75.

3. Past or current history of a clinically significant central nervous system disorder that may contribute to prodromal symptoms or confound their assessment.

4. Traumatic Brain Injury that is rated as 7 or above on the Traumatic Brain Injury screening instrument.

5. No current treatment with antipsychotic medication (unless it can be clearly demonstrated that the diagnostic prodromal criteria were present prior to the antipsychotic).

6. Must not have diagnostic prodromal symptoms that are clearly caused by an Axis 1 disorder, including substance use disorders, in the judgment of the evaluating clinician.

Other non-psychotic DSM-IV disorders will not be exclusionary (e.g. substance abuse disorder, major depression, anxiety disorders, Axis II Disorders) providing the disorder does not account for the diagnosis of prodromal symptoms.

2.2.2 FHR-Non Group

Inclusion Criteria

1. Must meet FHR-COPS inclusion criteria 1-3.
**Exclusion Criteria**

1. Same as FHR-COPS exclusion 1-6.

2. Must not meet diagnostic criteria for a psychosis risk syndrome as per COPS Criteria, or evidence any subthreshold psychotic symptoms.

**2.2.3 Healthy Controls**

**Inclusion Criteria**

1. Must meet FHR-COPS/FHR-Non inclusion criteria 1-2.

**Exclusion Criteria**

1. Same as all exclusion criteria for FHR-Non group 1-7.

2. Must not have a family history (in first-degree relatives) of schizophrenia, schizoaffective disorder, schizotypal personality disorder, or any other disorder involving psychotic symptoms.

**2.3 Procedure**

The healthy controls and the FHR-COPS participants were part of the NAPLS project which is ongoing and has been approved by the University of Calgary Conjoint Health Research Ethics Board. The addition of individuals who exclusively meet criteria for family history of psychosis was also approved by ethics as an amendment to the NAPLS project. The standard
procedures for NAPLS continued as usual. Individuals who responded to our recruitment efforts for the FHR component were screened on the phone and if suitable were invited in for an assessment to determine inclusion criteria. If it was determined at this point that the individual met criteria for a psychosis risk syndrome, they were offered the opportunity to participate in the NAPLS project. Individuals who met FHR criteria were invited to participate in the study. All interested individuals signed informed consent.

Participants were assigned a clinical and neurocognitive rater. Clinical raters conducted semi structured interviews to assess symptom severity, global levels of functioning, social and role functioning, self reported anxiety, schemas about self and others, perceived discrimination, experience of trauma, cannabis use and history of head injury. The WASI was part of a neurocognitive battery and was also administered by trained raters. Reliability of the diagnostic interview has been described elsewhere (Addington et al., submitted).

2.4 Measures

The Structured Clinical Interview for DSM-IV Disorders (SCID-1) (First et al., 1994) was used to determine the presence of any Axis 1 disorders. The Structured Interview for Prodromal Symptoms (SIPS) (McGlashan et al., 2010) was used to determine the presence and severity of prodromal symptoms. The SIPS consists of questions organized by 19 items in 4 domains of prodromal psychopathology; attenuated positive symptoms, negative symptoms, disorganized symptoms, and general symptoms. The SIPS interview is used to detect the severity of
prodromal symptoms, and rated from a scale of 0-6. Having a score of 6 on the positive symptoms reflects a score considered to be at psychotic level intensity.

Depression was measured using the *Calgary Depression Scale for Schizophrenia (CDSS)* (Addington et al., 1993). This interview was designed to assess depression in individuals with schizophrenia and other psychotic disorders. This scale is widely used with individuals with schizophrenia (Addington et al., 1990) and has demonstrated good psychometric properties. It is specifically designed to differentiate depression from negative symptoms. There are 9 questions which are scored from 0 (absent) to 3 (severe) creating an overall total score.

*The Cannon-Spoor Premorbid Adjustment Scale (PAS)* (Cannon-Spoor et al., 1982) was used as a measure of early social functioning. The PAS provides information on four areas of development; sociability, peer relationships, ability to function outside the family, and capacity to form intimate sexual relations. These are assessed across four developmental time periods – childhood, early and late adolescence, and adulthood. The scores range from 0-6 with a lower score indicating better functioning.

Global functioning was assessed using *The Global Assessment of Functioning (GAF) Scale* (Endicott et al., 1976). The GAF is a scale from 0-100, where a score of greater than 70 indicates good functioning, or mildly abnormal psychosocial situation. Social and role functioning was assessed using the *Global Functioning Scale: Social & Global Functioning Scale: Role (GF:S & GF:R)* (Cornblatt et al., 2007b; Cornblatt et al., 2007a). These scales were developed by Cornblatt and colleagues specifically for the NAPLS project, and are used to determine interpersonal skills and independent school/employment or homemaking capabilities in the
prodromal phase of psychosis. Both scales are scored from 1-10 (10 indicating the highest level of functioning). They have high inter-rater reliability and construct validity, are easy to use and can detect functional changes over time (Cornblatt et al., 2007a).

The Family Interview for Genetics Studies (FIGS) (Maxwell, 1996) was used to determine a family history of mental illness, as well as the presence of a psychotic disorder in a first degree relative.

The Brief Core Schema Scale (BCSS) (Fowler et al., 2006) was used to determine evaluations of the self and others. The BCSS has 24 items concerning beliefs about the self and others that are assessed on a 5-point rating scale (0–4). Four scores, each with six items, are obtained: negative-self, positive-self, negative-others and positive-others. This has been shown to be an appropriate scale for a prodromal for psychosis population in that negative beliefs about self and others were significantly associated with attenuated positive symptoms (Addington and Tran, 2009).

The Perceived Discrimination (Janssen et al., 2003) scale was used to query if individuals have ever experienced discrimination over the past year, and lifetime because of their skin colour, ethnicity, gender, age, appearance, disability, or sexual orientation.

Experience of trauma and abuse was captured using the Childhood Trauma and Abuse Scale (Janssen et al., 2004). This is a semi-structured interview in which the interviewer enquires about trauma and abuse before the age of 16. The participant is asked about any psychological or physical bullying, as well as any emotional, physical, psychological or sexual abuse.
The Social Interaction Anxiety Scale (SIAS) & Social Anxiety Scale (SAS) (Olivares et al., 2001) captured self-reported anxiety levels. These scales demonstrate good psychometric properties and have been used in patients with psychosis. They demonstrate reliability with both adult and adolescent populations.

The Traumatic Brain Injury (TBI) Interview (AbdelMalik et al., 2003) was used to assess previous history of head injury. Participants were asked a series of probing questions to query whether they ever had any head injuries and if they ever lost consciousness from any head injuries. Severity was recorded on a scale from 1; no head injury to 8; loss of consciousness or coma lasting more than 6 hours.

Cognition scores were captured using the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler D, 1987). This measure consists of four subtests: two verbal and two performance. The verbal test assesses expressive vocabulary and abstract verbal reasoning. The performance test assesses visual construction skills and visual reasoning. An IQ score was created using a combination of two of these subtests (one verbal and one performance).

A new measure was developed to assess Cannabis Use based on commonly used measures and interview questions in the literature (Henquet et al., 2005a; Arseneault et al., 2002; Caspi et al., 2005). The scale consists of 8 questions which enquire if cannabis has ever been used, how many times it has been used, if they are a current or past user, the age at first use, how often it is used, the pattern of use, the context it is used in (i.e. socially or alone) and the time of day it is used most frequently (i.e. morning, evening or both).
Other drug and alcohol use was recorded using the *Alcohol and Drug Use Scale* (Drake et al., 1996). This scale records both level of use ranging from scores of 1 (abstinent) to 5 (dependence) as well as frequency of use ranging from scores of 0 (no use) to 5 (almost daily). It includes alcohol, tobacco, marijuana, cocaine, opiates, PCP, amphetamines, MDMA, GHB, huffing, and hallucinogens. Substances not listed but that are mentioned by the participant are also recorded.

### 2.5 Statistical Analyses

All outcome variables were examined prior to analyses for distribution. For each group graphical and tabular methods were used to describe the demographic and baseline values for outcome measures. Univariate tabulations included the mean, standard deviation, median and range. Bivariate tabulations included Pearson or Spearman correlation coefficients for association among all outcome measures. Graphical measures included scatter plots, box plots or frequency histograms. These simple computations were important for informal familiarization and visualization of the data values and served as a complement to the other analyses. Means were compared using the Student t-test and ANOVA. Categorical variables, proportions and percentages were compared using Kruskal-Wallis, Mann-Whitney, or chi-square tests.

Participant’s baseline characteristics were compared in order to control for any potential confounders such as age or gender. Further comparisons were made in order to test the first hypothesis between the FHR-COPS, FHR-Non and healthy controls. The groups were compared
on the following measures of social risk; immigration status, early childhood trauma, brain injury, IQ, perceived discrimination and cannabis use. For the secondary hypothesis, the three groups were compared on measures of functioning (current GAF, social, role and premorbid functioning) and on measures of psychopathology (depression, self reported anxiety and schemas).

In order to further investigate which risk factors were potential predictors of having a psychosis risk syndrome, a binary logistic regression was performed with belonging to either the FHR-COPS or FHR-Non group as the dependent variable. All the possible predictors with a p-value of less than 0.05 in the univariate analysis were considered in the model.
Chapter Three: Results

3.1 Demographic Characteristics

The sample consisted of 75 participants; 25 FHR-COPS, 25 FHR-Non and 25 healthy controls. Baseline demographic information is presented in Table 1. Eleven (44%) of the FHR-COPS participants met criteria for both APS and GRD, nine (36%) met APS, and five (20%) met the GRD criteria. None of the FHR-COPS participants met BIPS criteria. The majority of participants were unmarried, currently enrolled as a student, and female. There were no significant differences between the three groups on any of the demographic variables assessed.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Healthy Controls n=25</th>
<th>FHR-Non n=25</th>
<th>FHR-COPS n=25</th>
<th>Test Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>19.64 (5.23)</td>
<td>20.76 (5.85)</td>
<td>17.88 (3.24)</td>
<td>2.18</td>
</tr>
<tr>
<td>Years of Education</td>
<td>12.44 (4.32)</td>
<td>12.00 (3.27)</td>
<td>11.04 (2.77)</td>
<td>1.01</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td>10 (40.0%)</td>
<td>15 (60.0%)</td>
<td>10 (40.0%)</td>
<td>15 (60.0%)</td>
</tr>
<tr>
<td>Race</td>
<td>Asian</td>
<td>West/Central Asia/Middle East</td>
<td>White</td>
<td>Interracial</td>
</tr>
<tr>
<td></td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (4.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td></td>
<td>22 (88.0%)</td>
<td>21 (84.0%)</td>
<td>19 (76.0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 (0.0%)</td>
<td>3 (12.0%)</td>
<td>3 (12.0%)</td>
<td></td>
</tr>
<tr>
<td>Marital Status</td>
<td>Single never married</td>
<td>Married/Common Law</td>
<td>Living with significant other</td>
<td>24 (96.0%)</td>
</tr>
<tr>
<td></td>
<td>24 (96.0%)</td>
<td>22 (88.0%)</td>
<td>24 (96.0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 (0.0%)</td>
<td>2 (8.0%)</td>
<td>1 (4.0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (4.0%)</td>
<td>1 (4.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currently working</td>
<td>Yes, full time</td>
<td>Yes, half time</td>
<td>Yes, full time</td>
<td>Yes, half time</td>
</tr>
<tr>
<td></td>
<td>6 (24.0%)</td>
<td>3 (12.0%)</td>
<td>6 (24.0%)</td>
<td>5 (20.0%)</td>
</tr>
</tbody>
</table>
Group comparisons on social risk factors between the three groups were conducted using ANOVA for continuous variables and Kruskal-Wallis, chi-square, and Mann-Whitney for categorical variables. These results are presented in Table 2. Post-hoc analysis revealed significant differences between the FHR-COPS and FHR-Non on the age first tried cannabis and IQ.

### Table 2. Group Comparisons of Social Risk Factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Healthy Controls (n=25)</th>
<th>FHR-Non (n=25)</th>
<th>FHR-COPS (n=25)</th>
<th>Test Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (%)</td>
<td></td>
<td>Number (%)</td>
<td></td>
</tr>
<tr>
<td><strong>Immigration Status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Born in Canada</td>
<td>21 (84.0%)</td>
<td>24 (96.0%)</td>
<td>21 (88.0%)</td>
<td>7.21</td>
</tr>
<tr>
<td>1st Generation Migrant</td>
<td>3 (12.0%)</td>
<td>1 (4.0%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>2nd Generation Migrant</td>
<td>1 (4.0%)</td>
<td>0 (0.0%)</td>
<td>3 (12.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Trauma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychological Bullying</td>
<td>10 (40.0%)</td>
<td>14 (56.0%)</td>
<td>18 (75.0%)</td>
<td>6.12*</td>
</tr>
<tr>
<td>Physical Bullying</td>
<td>5 (20.0%)</td>
<td>8 (32.0%)</td>
<td>8 (32.0%)</td>
<td>1.32</td>
</tr>
<tr>
<td>Emotional Neglect</td>
<td>3 (12.0%)</td>
<td>10 (40.0%)</td>
<td>13 (52.0%)</td>
<td>9.95**</td>
</tr>
<tr>
<td>Psychological Abuse</td>
<td>2 (8.0%)</td>
<td>11 (44.0%)</td>
<td>12 (50.0%)</td>
<td>11.42*</td>
</tr>
<tr>
<td>Physical Abuse</td>
<td>3 (12.0%)</td>
<td>9 (36.0%)</td>
<td>8 (32.0%)</td>
<td>4.37</td>
</tr>
<tr>
<td>Sexual Abuse</td>
<td>0 (0.0%)</td>
<td>4 (16.0%)</td>
<td>5 (20.0%)</td>
<td>5.50</td>
</tr>
<tr>
<td><strong>Total Bullying</strong></td>
<td>0.60 (0.76)</td>
<td>0.88 (0.72)</td>
<td>1.08 (0.72)</td>
<td>5.47</td>
</tr>
<tr>
<td><strong>Total Trauma</strong></td>
<td>0.84 (1.25)</td>
<td>2.24 (1.79)</td>
<td>2.67 (1.76)</td>
<td>17.68</td>
</tr>
</tbody>
</table>
3.3 Psychopathology & Functioning

Table 3 presents the ANOVA results conducted between all three groups on psychopathology and functioning as indicated by the CDSS, SIAS, SAS, schemas, current GAF, social and role functioning and premorbid functioning. In terms of psychopathology, significant differences were revealed between the FHR-COPS and FHR-Non group on total scores of anxiety as well as negative schemas about self. In terms of functioning, post-hoc analysis revealed significant differences between the FHR-COPS and FHR group on all variables of functioning with the exception of premorbid functioning which was only different between FHR-COPS and controls.
The groups were compared on SCID diagnoses. There were significant differences on several of the diagnoses. Results of significant diagnoses are presented in Table 4.

### Table 3. Group Comparisons of Psychopathology & Functioning

<table>
<thead>
<tr>
<th>Variable</th>
<th>Healthy Controls N=25</th>
<th>FHR-Non N=25</th>
<th>FHR-COPS N=25</th>
<th>Test Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>F Value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDSS</td>
<td>0.28 (0.74)</td>
<td>2.76 (3.81)</td>
<td>4.71 (4.35)</td>
<td>11.83****</td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIAS</td>
<td>7.08 (5.83)</td>
<td>18.76 (15.84)</td>
<td>27.63 (17.13)</td>
<td>13.57****</td>
</tr>
<tr>
<td>SAS</td>
<td>23.88 (3.45)</td>
<td>30.24 (13.24)</td>
<td>37.71 (10.47)</td>
<td>11.79***</td>
</tr>
<tr>
<td>Core Schemas</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative Self</td>
<td>0.28 (0.74)</td>
<td>3.04 (5.04)</td>
<td>6.46 (5.46)</td>
<td>12.72****</td>
</tr>
<tr>
<td>Negative Others</td>
<td>1.60 (3.07)</td>
<td>3.76 (5.57)</td>
<td>6.88 (4.68)</td>
<td>7.93****</td>
</tr>
<tr>
<td>Positive Self</td>
<td>17.56 (5.41)</td>
<td>13.68 (6.17)</td>
<td>11.92 (5.29)</td>
<td>5.89**</td>
</tr>
<tr>
<td>Positive Others</td>
<td>15.44 (5.85)</td>
<td>13.92 (5.20)</td>
<td>10.88 (4.32)</td>
<td>4.75**</td>
</tr>
<tr>
<td>GAF</td>
<td>88.00 (4.40)</td>
<td>80.00 (11.93)</td>
<td>46.00 (13.85)</td>
<td>117.04****</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>9.13 (0.99)</td>
<td>8.12 (1.36)</td>
<td>6.70 (1.46)</td>
<td>19.74****</td>
</tr>
<tr>
<td>Role Functioning</td>
<td>9.00 (1.06)</td>
<td>8.00 (2.02)</td>
<td>5.65 (2.42)</td>
<td>17.71****</td>
</tr>
<tr>
<td>Premorbid Functioning</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Childhood</td>
<td>0.13 (0.17)</td>
<td>0.16 (0.13)</td>
<td>0.25 (0.15)</td>
<td>3.67*</td>
</tr>
<tr>
<td>Early Adolescence</td>
<td>0.08 (0.10)</td>
<td>0.23 (0.15)</td>
<td>0.27 (0.13)</td>
<td>13.59****</td>
</tr>
<tr>
<td>Late Adolescence</td>
<td>0.06 (0.06)</td>
<td>0.23 (0.14)</td>
<td>0.33 (0.15)</td>
<td>18.10****</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001

*a* = significantly different from controls, *b* = significantly different from FHR-COPS

### Table 4. Group Comparisons on SCID Results

<table>
<thead>
<tr>
<th>SCID Diagnosis</th>
<th>Healthy Controls N=25</th>
<th>FHR-Non N=25</th>
<th>FHR-COPS N=25</th>
<th>X²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Mood Disorder</td>
<td>0 (0.0%)</td>
<td>5 (20.0%)</td>
<td>10 (40.0%)</td>
<td>13.16**</td>
</tr>
<tr>
<td>Lifetime Mood Disorder</td>
<td>1 (4.0%)</td>
<td>6 (24.0%)</td>
<td>9 (36.0%)</td>
<td>8.24*</td>
</tr>
<tr>
<td>Lifetime Alcohol Disorder</td>
<td>0 (0.0%)</td>
<td>1 (4.0%)</td>
<td>10 (40.0%)</td>
<td>20.32****</td>
</tr>
<tr>
<td>Current Social Phobia</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>3 (12.0%)</td>
<td>6.51*</td>
</tr>
<tr>
<td>Lifetime Reading Disorder</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>3 (12.0%)</td>
<td>6.80*</td>
</tr>
<tr>
<td>Current Schizotypal Personality</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>3 (12.0%)</td>
<td>6.51*</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01, ***p<0.0001*
3.4 Regression Analysis

The results of the logistic regression analysis are presented in Table 5. All significant variables between the FHR-COPS and FHR-Non group from the univariate analysis presented in Table 2 were included in the model. An analysis was conducted to determine which risk variables predicted belonging to the FHR-COPS groups. These two variables are correlated at r=0.61. There is no formal way in SPSS to test for multicollinearity but Tabachnic and Fidell (Tabachnick and Fidell, 2001) only suggest concerns with respect to r values greater than 0.7. The Omnibus Tests of Model Coefficients is significant (chi square =7.91  df, 2  p=0.02 ) which suggests a goodness of fit. This is supported by the Hosmer and Lemeshow Test (chi square =7.51, p= 0.28). The Cox & Snell R square = 0.26 and the Nagelkerke R square = 0.35, which suggests that the amount of variance in the dependent variable explained by the model is between 26% and 35%. The sensitivity of the model is 80% and the specificity is 64%. The positive predictive value is 73%. The only variable that contributed significantly and thus is a major factor in determining whether an individual at family high risk meets criteria for a Psychosis Risk Syndrome is a young age at first using cannabis.

<table>
<thead>
<tr>
<th>Outcome Variable</th>
<th>OR</th>
<th>B</th>
<th>SE</th>
<th>Wald</th>
<th>df</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age first tried cannabis</td>
<td>0.44</td>
<td>-0.82</td>
<td>0.42</td>
<td>3.82</td>
<td>1</td>
<td>0.195-1.003</td>
<td>0.05</td>
</tr>
<tr>
<td>WASI IQ</td>
<td>1.00</td>
<td>0.02</td>
<td>0.048</td>
<td>0.02</td>
<td>1</td>
<td>0.912-1.102</td>
<td>0.96</td>
</tr>
</tbody>
</table>
Chapter Four: Discussion

The overall aim of this project was to determine the differences between individuals with a family high risk of psychosis who met criteria for a psychosis risk syndrome (FHR-COPS) to family high risk individuals that did not in terms of social risk factors (FHR-Non). The primary hypothesis was that the FHR-COPS individuals would evidence more social risk factors defined as previous traumatic experiences, greater sense of discrimination, ever having had a head injury, cannabis use before age 15 and lower IQ compared to FHR-Non individuals and to healthy controls. The primary hypothesis was partially supported by the results in that individuals with a psychosis risk syndrome had a significantly lower IQ score as well as began smoking cannabis at an earlier age compared to FHR-Non individuals. Multivariate analysis demonstrated that the onset of cannabis use at an earlier age was a significant predictor of belonging to the FHR-COPS group. With respect to other social risk factors, there were no differences between FHR groups on previous traumatic experiences, past history of having had a head injury, or levels of perceived discrimination.

Relative to healthy controls, FHR-COPS individuals evidenced more psychological bullying, emotional neglect, psychological abuse, overall levels of total trauma, reported a greater sense of perceived discrimination, and reported more head injuries. Interestingly, and although not part of the hypotheses, it was found that the FHR-Non group also significantly differed from controls in that they reported more emotional neglect, psychological abuse, overall levels of total trauma, and a greater sense of perceived discrimination in the last year compared to controls.
The main finding on early cannabis use as a significant predictor supports other studies that indicate an association between early cannabis use and a greater risk of developing psychosis or psychotic like symptoms (Konings et al., 2008; Arseneault et al., 2002; Stefanis et al., 2004; Dragt et al., 2010; Galvez-Buccollini et al., 2012). The current finding is also unique in that it is the first of its kind to investigate the early use of cannabis in a sample of FHR individuals differentiated by the presence of having a psychosis risk syndrome. This finding was further strengthened by the fact that the two FHR groups did not differ on either their past frequency or current use of cannabis, offering more support to the argument that the age the use began may be more relevant than the cumulative effects of the cannabis use for psychosis. One suggested explanation for this finding is that early cannabis use creates an increased vulnerability to $\Delta^9$-tetrahydrocannabinol (THC) during the critical phases of brain maturation, such as in early puberty, which in turn has an association to the development of psychosis or psychotic like symptoms (Casadio et al., 2011). Of course it could also be argued that individuals who began smoking cannabis earlier in this study were simply just more prone to smoking cannabis earlier due to other reasons not investigated, or were doing so in order to ‘self medicate’ or alleviate some of their experienced symptoms. However, it should be noted that the self medication theory is unlikely in the current sample as the initiation of cannabis use occurred in advance of the onset of attenuated positive symptoms or drop in functioning for the large majority of FHR-COPS participants who reported using cannabis in this study.

Although not included in the hypothesis, it was also found that the two FHR groups differed from controls on both the past frequency and current use of cannabis. This provides
support for the body of literature that looks at gene-environment interactions and the risk of cannabis use in vulnerable populations (Henquet et al., 2008; Caspi et al., 2005; Genetic Risk and Outcome in Psychosis (GROUP) Investigators, 2011). More support for the negative effects of cannabis use among individuals with a family history of psychosis comes from recently published data from the Edinburgh High Risk study which revealed that in 57 non psychotic relatives of individuals with schizophrenia, those who had used cannabis between two assessment points had significant reductions in thalamic brain volume (Welch et al., 2011). This finding held even after other illicit drugs were removed from the analysis.

The main hypothesis of this study was further supported in that FHR-COPS groups had a significantly lower IQ score compared to FHR-Non and controls. However, while low IQ did not prove to be an independent predictor in the current study from the results of the regression, the significant model and differences displayed in the univariate analysis should not be discounted for future research. It is well established in the literature that non psychotic family members of individuals with psychosis evidence lower IQ scores or poorer cognitive performance compared to healthy controls or at least intermediate to individuals with schizophrenia and healthy controls (de la Serna et al., 2011b; Scala et al., 2012). However, in the current sample although the FHR-COPS individuals had a lower IQ compared to controls, there were no differences between FHR-Non and controls, indicating this was a specific difference only for FHR-COPS individuals in this sample.

Contrary to the first hypothesis, the two FHR groups did not differ on the amount of trauma experienced before the age of 16. When compared to controls in this study, and other general
population studies (Frans et al., 2005; Briere and Elliott, 2003) both FHR groups reported similar, relatively high levels of each type of trauma and total trauma. While these high reported levels were somewhat surprising, this was not entirely unexpected given other reports in the research which show that FHR individuals experience less trauma compared to their affected family members, but more trauma compared to healthy controls (Heins et al., 2011). According to one study, an explanation for this could be that it may not necessarily be the amount of trauma or the cumulative effects of the trauma that contribute to the association to later psychosis, but rather the perception of the intention to harm, or element of threat that may be more or equally important (Arseneault et al., 2011).

The secondary hypothesis was that the FHR-Non group would occupy an intermediate position relative to the FHR-COPS group and healthy controls in terms of the level of functioning and severity of psychopathology. This was partially supported in the current study in that the data showed a trend from highest functioning and least severe levels of psychopathology in the controls, followed by the FHR-Non group, and finally the worst functioning and most severe levels of psychopathology in the FHR-COPS group. This finding is somewhat consistent with current findings in the literature which look at functioning and psychopathology in siblings or offspring of individuals with psychosis (Keshavan et al., 2008; de la Serna et al., 2011b). However the current findings are more specific in that the current sample of FHR individuals were further distinguished by having a psychosis risk syndrome.

With respect to psychopathology, when compared to the FHR-Non group, the FHR-COPS group showed significantly higher levels of self reported anxiety as well as more negative
schematic beliefs about the self. The FHR-COPS group also reported the most Axis I disorders compared to both the FHR-Non and control groups. However, the only significant difference between the FHR groups on Axis I disorders was that the FHR-COPS group was more likely to have met criteria for a lifetime alcohol use disorder.

In terms of functioning, the FHR-COPS group displayed lower levels of both social and role functioning as well as overall lower levels of global functioning as indicated by the GAF. This is perhaps not surprising given that one form of entry into the FHR-COPS group required having deterioration in functioning. Therefore, the analyses on functioning variables were rerun excluding the individuals who met criteria for GRD. The two FHR groups still differed significantly on overall GAF scores as well as role functioning but no longer on social functioning. Both groups still remained significantly different to controls on social and role functioning as well as overall global functioning as indicated by the GAF (see Appendix A).

It is noteworthy that the FHR-COPS group had significantly worse early premorbid childhood functioning compared to controls and that FHR-Non participants did not differ from controls on early premorbid childhood functioning. Although this could be confounded by retrospective report in the current study, this still gives rise to the question on whether or not these functional difficulties begin early for those who later develop a psychosis risk syndrome.

4.1 Limitations

There are several limitations in this study. Firstly, the sample size was small with only 25 in each group. Nonetheless, significant differences were observed between the groups and
further to this significant differences were also observed to controls. Secondly, the current data is cross sectional. Thus it is possible that some of the FHR-COPS individuals will still develop symptoms or a decline in their functioning.

Thirdly, although it was assessed whether trauma had or had not occurred, data determining the severity, frequency or timing of trauma is not available. A fourth limitation was that the level of cannabis use was not physiologically tested and it is therefore possible that participants that did not endorse using cannabis in fact were. A fifth potential limitation was that as some of the measures relied on retrospective report, such as the lifetime cannabis use, trauma before age 16, or premorbid functioning and therefore could have been over or underestimated due to recall errors. A sixth limitation is that due to the lack of diversity in the current sample, other important risk factors such as immigration or urbanicity could not be investigated. However, as much of the research on migration now points towards the perception of feeling discriminated against (regardless of actual levels of discrimination) it is possible that the measure used on perceived discrimination was an accurate replacement for the current sample. Finally, only 72% of family member diagnoses of psychosis could be confirmed in the current study via SCID interview or formal records. The remaining diagnoses were obtained from a trained nurse who interviewed either the participant or other family members to provide the information that unofficially confirmed diagnoses in the remaining 28% of cases.
4.2 Future Work

The study of individuals with a family history who may or may not have early signs or symptoms could be a valuable way to understand developing psychosis. Future work should consider larger samples that could potentially be followed longitudinally to determine if those at FHR with no symptoms later develop subthreshold symptoms. With larger samples other means of dividing the groups could include individuals who meet schizotypy criteria or have psychotic like experiences and not just using the strict prodromal criteria. Larger future studies could also consider the inclusion of various biomarkers. For example better understanding the role genes play in cannabis use may provide valuable information regarding the mechanisms of use or considering in these samples the role of cortisol in relation to stressful life events.
Chapter Five: Conclusions

In conclusion, the results suggest that in this sample, FHR individuals with a psychosis risk syndrome compared to those who did not, began smoking cannabis at an earlier age, had a lower IQ and evidenced more anxiety, negative schemas about the self and poorer functioning. In addition to this, the most predictive social risk factor for belonging to the FHR-COPS group was the onset of cannabis use at an earlier age. Of course not all the individuals in this study will go on to develop psychosis, however, the findings provide implications for early intervention and prevention for those who are already at some risk of developing psychosis based on family history. The finding on cannabis may provide further awareness and public knowledge regarding the additional risks associated with early cannabis use in a vulnerable population and its association to psychosis.
Chapter Six: References


Fish, B., 1960. Involvement of the central nervous system in infants with schizophrenia. Arch Neurol. 2, 115-121.


Maxwell, M. E., 1996. FIGS. Clinical Neurogenetics Branch, Intramural Research Program., Bethesda Maryland, NIMH.


## Appendix A. Group Comparisons of Functioning after GRD Participants Removed

<table>
<thead>
<tr>
<th>Variable</th>
<th>Healthy Controls n=25</th>
<th>FHR- Non n=9</th>
<th>FHR- COPS n=25</th>
<th>Test Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>F Value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GAF</td>
<td>87.92 (4.40)</td>
<td>53.89 (13.49)</td>
<td>40.66**</td>
<td></td>
</tr>
<tr>
<td>Social Functioning</td>
<td>9.13 (0.99)</td>
<td>7.71 (1.60)</td>
<td>5.54*</td>
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</tr>
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<td>Role Functioning</td>
<td>9.00 (1.06)</td>
<td>6.14 (2.41)</td>
<td>7.67*</td>
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<tr>
<td>Premorbid Functioning</td>
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<td></td>
</tr>
<tr>
<td>Childhood</td>
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<td>0.16 (0.13)</td>
<td>1.88</td>
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<td>Early Adolescence</td>
<td>0.08 (0.10)</td>
<td>0.23 (0.15)</td>
<td>9.45**</td>
<td></td>
</tr>
<tr>
<td>Late Adolescence</td>
<td>0.06 (0.06)</td>
<td>0.23 (0.14)</td>
<td>10.70**</td>
<td></td>
</tr>
</tbody>
</table>

*p<0.01, **p<0.0001

*a* = significantly different from controls,  
*b* = significantly different from FHR-COPS