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Predictors of a clinical high risk status among individuals with a family history of psychosis

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Abstract

Background—Risk for psychosis can be assessed on the basis of genetic risk, referred to in the literature as family high risk (FHR) or through the presence of clinical high risk symptoms (CHR). Recent studies have also shown that certain risk factors (i.e. trauma, cannabis, migration) may play a role in the development of psychosis, possibly in combination with one another and in particular in combination with a family history of psychosis. It is unknown which risk factors may play a role in the prediction of CHR status among individuals whom are already genetically vulnerable. This study compared FHR individuals who also met CHR criteria to FHR individuals who did not on various risk factors, psychopathology and functioning.

Method—Participants were 25 who met FHR and CHR criteria (FHR + CHR) as determined by Structured Interview for Prodromal Syndromes, 25 who met only FHR criteria (FHR-non-CHR), and 25 healthy controls. A binary logistic regression was performed to determine the best predictors of belonging to the FHR + CHR group.

Results—FHR + CHR and FHR-non CHR were significantly different on measures of age first tried cannabis ($F = 3.65$, $p < 0.05$) and IQ ($F = 3.32$, $p < 0.05$). FHR groups also differed on self-reported anxiety ($F = 11.79$, $p < 0.001$) and current scores of social ($F = 19.74$, $p < 0.0001$) and role ($F = 17.71$, $p < 0.0001$) functioning. The most significant predictor of belonging to the FHR + CHR group was an earlier age of cannabis use ($OR = 0.44$, $p = 0.05$).

Conclusion—These preliminary results are promising in determining potential risk factors for the development of psychosis in those who are at risk for psychosis on the basis of a family history.

Keywords

Psychosis; Risk; Family history; Prodrome; Risk factors

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Contributors

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Conflict of interest

There are no conflicts of interests for either author.

1. Introduction

One way to determine an individual's risk for developing psychosis is based on the relationship to an affected individual, usually a first-degree relative and often a parent (Cannon et al., 2003). The risk here for developing psychosis is approximately 10% compared to 1% in the general population, risk that increases with the degree of the genetic relationship (de la Serna et al., 2011). There have been several seminal studies of individuals with a family risk of psychosis (FHR) (Fish, 1960; Nagler et al., 1985; Mednick et al., 1987; Erlenmeyer-Kimling et al., 2000; Johnstone et al., 2005). A review of this literature suggests that around 25–60% of high risk children display poor timing of developmental milestones, and deficits in cognition social functioning, attention and information processing (Cannon et al., 2003). While there are many advantages of these FHR studies, such as the power of prospective data, standard assessments, and true blindness as to outcome, these types of studies take a long time with both subject and investigator dropout and what once may have been state of the art tools easily become out-dated.

Recent research focuses on those who may be at risk of developing psychosis based on clinical symptoms and thus experiencing a potential prodrome for psychosis (Addington and Heinssen, 2012). Reliable criteria have been developed (McGlashan et al., 2010) and researchers are able to prospectively follow the course of the illness with the goal of being able to distinguish differences between those who go on to develop psychosis and those who do not. A recent meta-analysis indicates that approximately 29% of these at risk individuals will go on to develop a full blown illness within two years (Fusar-Poli et al., 2012). Since risk is determined on the basis of clinical symptoms these individuals are considered to be at clinical high risk (CHR) of developing psychosis.

There is a growing literature linking risk for psychosis to certain biological and psychosocial risk factors such as urban upbringing (Krabbendam and van Os, 2005; Kelly et al., 2010), migration (Veling and Susser, 2011), discrimination or more likely perceived discrimination (Janssen et al., 2003; Karlsen et al., 2005), history of trauma in childhood (Arseneault et al., 2011; Bendall et al., 2013), cannabis use and the age of first using cannabis (Arseneault et al., 2002; Stefanis et al., 2004; Henquet et al., 2005, 2008; Konings et al., 2008), traumatic brain injury (AbdelMalik et al., 2003), obstetric complications (Cannon et al., 2002), paternal age at conception (Miller et al., 2011) as well as a wide range of other factors such as infections (Torrey et al., 2012), motor dysfunction (Dickson et al., 2012), or internalizing and externalizing disorders (Tarbox and Pogue-Geile, 2008). There is also evidence that individuals that later develop schizophrenia display clinically significant intellectual impairments (Reichenberg et al., 2006) and a recent systematic review found that low IQ was among one of the strongest antecedents of schizophrenia (Matheson et al., 2011).

It has further been suggested that many of these factors are working in combination with one another (van Os et al., 2004; Houston et al., 2008; Konings et al., 2012) or additively (Cougnard et al., 2007; Harley et al., 2009; Kuepper et al., 2011) to even further increase risk of developing psychosis. Furthermore, these types of interactions have been reported in some FHR studies, suggesting that environmental factors may synergistically combine with pre-existing psychosis liability to cause symptoms of psychosis (Mirsky et al., 1985; Cannon

and Mednick, 1993; van Os et al., 2008; GROUP, 2010). Thus, if there is a combination of factors that may explain why some individuals at FHR of psychosis go on to develop the illness and some do not, it may be important to consider why some individuals at FHR develop subthreshold symptoms and why some do not. However, since many of the early FHR studies did not distinguish between those who had subthreshold symptoms and those who did not, it is possible that there may be the same synergy between family risk and other risk factors to predict CHR status.

The overall purpose of this project was to determine differences between individuals at FHR of psychosis who have developed subthreshold psychotic symptoms, that is, are at CHR for psychosis and FHR individuals who do not. The primary hypothesis is that the FHR group at CHR of psychosis would evidence more 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 individuals who do not meet CHR criteria. Secondly, the samples will be compared on functioning and psychopathology. A sample of healthy controls (HC) will be included to aid interpretability of results; particularly should the two FHR groups not differ on a given variable.

2. Methods

2.1. Participants

The sample consists of 50 participants with a family high risk of psychosis; 25 of whom were at clinical high risk of psychosis (FHR + CHR), 25 with no clinical high risk symptoms (FHR-non-CHR) and 25 healthy controls with neither a family history of psychosis or evidence of CHR symptoms. All participants were between the ages of 12 and 35 and were required to understand and sign informed consent. The FHR + CHR group and the healthy controls were recruited as part of the ongoing North American Prodrome Longitudinal Study 2 (NAPLS 2) at the Calgary site. FHR participants all had a first degree relative with a psychotic illness. Exclusion criteria were not meeting criteria for any current or lifetime axis I psychotic disorder, no prior history of treatment with an antipsychotic, IQ < than 70 or past and no current history of a clinically significant central nervous system disorder. The FHR + CHR participants met the Criteria of Prodromal Syndromes (COPS) using the Structured Interview for Prodromal Symptoms (SIPS) (McGlashan et al., 2010) and the FHR-non-CHR had no evidence of current or past subthreshold psychotic symptoms. The FHR-non-CHR participants were recruited from a variety of sources. Notices were posted in mental health clinics as well as other community settings and mass emails were sent out to various departments throughout the University. Further details on ascertainment, inclusion and exclusion criteria have been described in detail elsewhere (Addington et al., 2012). The distribution of affected family member was as follows; for the FHR + CHR sample: mother (n = 7, 28%), father (n = 10, 40%), brother (n = 5, 20%), or sister (n = 3, 12%) with psychosis. For the FHR-non-CHR group: mother (n = 11, 44%), father (n = 5, 20%), brother (n = 8, 32%), or sister (n = 1, 4%) with psychosis. Groups did not significantly differ on the distribution of affected family member.

2.2. Measures

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 *Structured Clinical Interview for DSM-IV Disorders (SCID-1)* (First et al., 1995) was used to determine the presence of any axis 1 disorders and the *Structured Interview for Prodromal Syndromes (SIPS)* (McGlashan et al., 2010) was used to determine the presence and severity of prodromal symptoms. The COPS have three possible prodromal syndromes — attenuated positive symptom syndrome (APSS), genetic risk and deterioration (GRD) and/or brief intermittent psychotic syndrome (BIPS). APSS 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 state requires having a combination of both functional decline (at least a 30% drop in GAF score over the last month as compared to 12 months ago) and genetic risk; genetic risk refers to having either schizotypal personality disorder or a first-degree relative with a schizophrenia spectrum disorder. 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.

Clinical measures included the *Calgary Depression Scale for Schizophrenia (CDSS)* (Addington et al., 1993) and the *Social Interaction Anxiety Scale (SIAS)* & *Social Anxiety Scale (SAS)* (Olivares et al., 2001). Functioning was assessed using the *Global Assessment of Functioning (GAF) Scale* (Endicott et al., 1976), the *Global Functioning Scale: Social & Global Functioning Scale: Role (GF:S & GF:R)* (Cornblatt et al., 2007) and *The Cannon-Spoor Premorbid Adjustment Scale (PAS)* (Cannon-Spoor et al., 1982).

The *Perceived Discrimination Scale* (Janssen et al., 2003) captures whether or not individuals believe they have experienced discrimination in the past year or in their lifetime because of their skin color; ethnicity; gender; age; appearance; disability; sexual orientation; religion; or other reason (respondents answer yes or no to each item). Frequency and severity of cannabis use was rated with the *Alcohol and Drug Use Scale* (Drake et al., 1996) which categorically measures both the level of substance use in the last month (1 = abstinent, 2 = use without impairment, 3 = abuse, 4 = dependence, 5 = dependence with institutionalization) as well as frequency of use in the last month (0 = no use, 1 = 1–2 in past month, 2 = 3–4 in past month, 3 = 1–2 per week, 4 = 3–4 per week, 5 = almost daily). Based on commonly used measures and interview questions in the literature (Arseneault et al., 2002; Caspi et al., 2005; Henquet et al., 2005) we also enquired if the participants had ever used cannabis, how many times it has been used, and age at first use. *Traumatic Brain Injury (TBI) Interview* (AbdelMalik et al., 2003) was used to assess previous history of head injury. Experience of trauma and abuse was captured using an adapted version of the *Childhood Trauma and Abuse Scale* (Janssen et al., 2004). This scale enquires about trauma and abuse before the age of 16. Respondents answer yes or no to ever experiencing any psychological or physical bullying, as well as any emotional, physical, psychological or sexual abuse. The

Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1987) was used to obtain a measure of IQ.

2.3. Procedure

The healthy controls and the FHR + CHR subjects were part of the ongoing NAPLS2 project at the Calgary site. Individuals who responded to our recruitment efforts were screened on the phone and if suitable were invited in for an assessment to determine inclusion criteria. All interested individuals signed informed consent. Participants were assigned a clinical and neurocognitive rater. Clinical raters conducted semi structured interviews. Reliability of the diagnostic interview is conducted on a yearly basis. Interclass correlation on the latest reliability for the Calgary site was 0.96.

2.4. Statistical analyses

The groups were compared on baseline characteristics to determine if there were any potential confounders such as age or gender. Chi-square tests were used to compare the three groups on sex, race, immigration status, marital status, employment status, each type of trauma, ever having had a head injury, or ever used cannabis. Kruskal–Wallis and Mann–Whitney tests were used to compare the groups on total trauma, total bullying, current level and frequency of cannabis use. ANOVAs were used to compare the groups on age, years of education, number of head injuries, age first tried cannabis, total cannabis use, IQ, perceived discrimination, and finally, measures of functioning (GAF, social/role, and premorbid functioning) and psychopathology (depression and self-reported anxiety).

To further investigate which risk factors were potential predictors of meeting clinical high risk criteria, a binary logistic regression was performed with group i.e. FHR + CHR or FHR-non-CHR as the dependent variable. All the possible risk predictors between the two FHR groups with a p-value of less than 0.05 from the univariate analyses described above were entered in the model.

3. Results

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

Group comparisons on risk factors between the three groups were conducted using ANOVA for continuous variables, chi-square for percentages, and Kruskal–Wallis and Mann–Whitney for non-parametric variables. These results are presented in Table 2. Post-hoc analysis revealed that the FHR + CHR group began smoking cannabis at an earlier age as well as had a lower IQ score compared to the FHR-non-CHR group. Although the two FHR groups did not differ on trauma or level and frequency of cannabis use from each other they did endorse more trauma than the healthy control group.

Using ANOVA, differences in psychopathology and functioning among the three groups are presented in Table 3. In terms of psychopathology the FHR + CHR group displayed significantly more anxiety compared to the FHR-non-CHR group. Both FHR groups had more depression than the controls. In terms of functioning, the FHR + CHR group had significantly lower functioning on all variables when compared to the FHR-non-CHR group, with the exception of premorbid functioning which was only different between FHR + CHR and controls.

The results of the logistic regression analysis are presented in Table 4. All significant variables between the FHR + CHR and FHR-non-CHR group from the univariate analysis presented in Table 2 were included in the model which included age first tried cannabis and IQ. These two variables are correlated at $r = 0.61$. 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%. Young age at first using cannabis is the only variable that made a significant contribution to the model.

Among the 25 FHR-non-CHR group there were 4 sibling pairs. All of the above analyses were re-run excluding one member of each of the pairs. The only change to significance levels was that the two FHR groups did not differ on IQ. Since IQ did not make a significant contribution to the model this does not affect the overall results and implications of the study.

4. Discussion

The main finding that early cannabis use is a significant predictor of belonging to the FHR + CHR group supports other studies that indicate an association between early cannabis use and a greater risk of developing psychosis or psychotic like symptoms (Arseneault et al., 2002; Stefanis et al., 2004; Konings et al., 2008; Dragt et al., 2012; Galvez-Buccollini et al., 2012). The current finding is also unique in that, to the best of our knowledge, this is the first study to investigate the early use of cannabis in a sample of FHR individuals differentiated by whether or not they meet CHR criteria. This finding was somewhat 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 Δ^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 be argued that individuals who began smoking cannabis earlier were doing so to self-medicate their early symptoms. However this is unlikely as in the current sample 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 + CHR participants who reported using cannabis in this study, a finding which has also been established in other CHR studies (Dragt et al., 2012).

The FHR + CHR group had a significantly lower IQ score compared to both the FHR-non-CHR group and the healthy controls. 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., 2011; Scala et al., 2012). However, in the current sample although the FHR + CHR individuals had a lower IQ compared to controls, there were no differences between FHR-non-CHR and controls, indicating this was a specific difference only for FHR + CHR individuals in this sample.

Contrary to our hypothesis, the two FHR groups did not significantly differ on immigration status, trauma, head injury or perceived discrimination. However, relative to healthy controls, FHR individuals reported a greater sense of perceived discrimination (FHR-non-CHR only in last year), more head injuries, as well as reported experiencing more traumatic events before age 16. Interestingly, both FHR groups reported similar, relatively high levels of each type of trauma and total trauma which may provide further support for one study that found that FHR individuals experience fewer traumas compared to their affected family members, but more trauma compared to healthy controls (Heins et al., 2011).

There was a trend for the FHR-non-CHR group to be intermediate to the healthy controls and the FHR + CHR on functioning and symptoms, although the differences were not always significant. Both FHR groups tended to have lower ratings on symptoms and functioning than the healthy controls which has been reported elsewhere (Keshavan et al., 2008; de la Serna et al., 2011). The two FHR groups differed on functioning and anxiety which is to be expected. It is note-worthy that the FHR + CHR group had significantly worse early premorbid childhood functioning compared to controls and that FHR-non-CHR 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 clinical high risk symptoms.

There are several limitations in this study. Firstly, the sample size was small with only 25 in each group. Nonetheless, significant differences were observed among the groups. Secondly, as the current data is cross sectional is possible that some of the FHR-non-CHR 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 may have been. A fifth limitation is that we only examined a few of the many risk factors reported in the literature such as immigration, urbanicity, obstetric complications, parental age, infections, motor dysfunction or internalizing/externalizing disorders could not be investigated. A sixth possible limitation is that the use of a statistical correction such as the Bonferroni method was not applied for multiple comparisons. A seventh limitation is that despite there being inconclusive evidence for this in the literature

(Addington and Barbato, 2012) it is possible that prodromal symptoms may have affected performance on IQ. 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.

In conclusion, these preliminary results suggest that the study of individuals with a family history who may or may not have early signs or symptoms could be a valuable way to further understand the development of psychosis. Future work first needs to study much larger samples of young people at FHR with and without subthreshold psychotic symptoms to expand on our results here. Secondly and more importantly, studies need to prospectively follow these young individuals to determine predictors, possibly biomarkers in addition to clinical, psychosocial and environmental variables of developing subthreshold symptoms.

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References

- AbdelMalik P, Husted J, Chow EWC, Bassett AS. Childhood head injury and expression of schizophrenia in multiply affected families. *Arch. Gen. Psychiatry.* 2003; 60:231–236. [PubMed: 12622655]
- Addington J, Barbato M. The role of cognitive functioning in the outcome of those at clinical high risk for developing psychosis. *Epidemiol. Psychiatr. Sci.* 2012; 21(4):335–342. [PubMed: 23174394]
- Addington J, Heinssen R. Prediction and prevention of psychosis in youth at clinical high risk. *Annu. Rev. Clin. Psychol.* 2012; 8:269–289. [PubMed: 22224837]
- Addington D, Addington J, Maticka-Tyndale E. Assessing depression in schizophrenia: the Calgary Depression Scale. *Br. J. Psychiatry.* 1993; 163:39–44.
- Addington J, Cadenhead K, Cornblatt B, Mathalon D, McGlashan T, Perkins D, Seidman L, Tsuang MT, Walker EF, Woods SW, Addington JA, Cannon TD. North American Prodrome Longitudinal Study (NAPLS 2): overview and recruitment. *Schizophr. Res.* 2012; 142:77–82. [PubMed: 23043872]
- Arseneault L, Cannon M, Poulton R, Murray RM, Caspi A, Moffitt TE. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. *Br. Med. J.* 2002; 325:1195–1199. [PubMed: 12446533]
- Arseneault L, Cannon M, Fisher HL, Polanczyk G, Moffitt TE, Caspi A. Childhood trauma and children's emerging psychotic symptoms: a genetically sensitive longitudinal cohort study. *Am. J. Psychiatry.* 2011; 168:65–72. [PubMed: 20952460]
- Bendall S, Alvarez-Jimenez M, Nelson B, McGorry P. Childhood trauma and psychosis: new perspectives on aetiology and treatment. *Early Interv. Psychiatry.* 2013; 7:1–4. [PubMed: 23356889]
- Cannon T, Mednick S. The schizophrenia high-risk project in Copenhagen: three decades of progress. *Acta Psychiatr. Scand. Suppl.* 1993; 370:33–47. [PubMed: 8452053]

- Cannon M, Jones PB, Murray RM. Obstetric complications and schizophrenia: historical and meta-analytic review. *Am. J. Psychiatry.* 2002; 159(7):1080–1092. [PubMed: 12091183]
- Cannon, M.; Tarrant, CJ.; Huttunen, J.; Jones, P. Child development and later schizophrenia: evidence from genetic high risk and birth cohort studies. In: Murray, R.; Jones, P.; Susser, E.; van, OsJ; Cannon, M., editors. *The Epidemiology of Schizophrenia*. New York: Cambridge University Press; 2003. p. 100–122.
- Cannon-Spoor H, Potkin S, Wyatt R. Measurement of premorbid adjustment in chronic schizophrenia. *Schizophr. Bull.* 1982; 8:470–484. [PubMed: 7134891]
- Casadio P, Fernandes C, Murray R, Di FM. Cannabis use in young people: the risk for schizophrenia. *Neurosci. Biobehav. Rev.* 2011; 35:1779–1787. [PubMed: 21530584]
- Caspi A, Moffitt TE, Cannon M, McClay J, Murray R, Harrington H, Taylor A, Arseneault L, Williams B, Braithwaite A, Poulton R, Craig IW. Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene $\times$ environment interaction. *Biol. Psychiatry.* 2005; 57:1117–1127. [PubMed: 15866551]
- Cornblatt B, Neindam T, Auther A, Smith C, Johnson JCT. Validation of two new measures of functional outcome in the schizophrenia prodrome. *Schizophr. Bull.* 2007; 33:688. [PubMed: 17440198]
- Cougnard A, Marcelis M, Myin-Germeys I, de GR, Vollebergh W, Krabbendam L, Lieb R, Wittchen HU, Henquet C, Spauwen J, van OJ. Does normal developmental expression of psychosis combine with environmental risk to cause persistence of psychosis? A psychosis proneness-persistence model. *Psychol. Med.* 2007; 37:513–527. [PubMed: 17288646]
- de la Serna E, Baeza I, Andres S, Puig O, Sanchez-Guistau V, Romero S, Bernardo M, Moreno D, Noguera A, Castro-Fornieles J. Comparison between young siblings and offspring of subjects with schizophrenia: clinical and neuropsychological characteristics. *Schizophr. Res.* 2011; 131:35–42. [PubMed: 21741217]
- Dickson H, Laurens KR, Cullen AE, Hodgins S. Meta-analyses of cognitive and motor function in youth aged 16 years and younger who subsequently develop schizophrenia. *Psychol. Med.* 2012; 42(4):743–755. [PubMed: 21896236]
- Dragt S, Nieman DH, Schultze-Lutter F, van der Meer F, Becker H, de Haan L, Dingemans PM, Birchwood M, Patterson P, Salokangas RK, Heinimaa M, Heinz A, Juckel G, Graf von Reventlow H, French P, Stevens H, Ruhrmann S, Klosterkötter J, Linszen DH. EPOS group. Cannabis use and age at onset of symptoms in subjects at clinical high risk for psychosis. *Acta Psychiatr. Scand.* 2012; 125(1):45–53. [PubMed: 21883099]
- Drake, RE.; Mueser, K.; McHugo, G. Clinical rating scales. In: Sederer, L.; Dickey, B., editors. *Outcomes Assessment in Clinical Practice*. Baltimore: Williams and Wilkins; 1996. p. 113–116.
- Endicott J, Spitzer R, Fleiss J, Cohen J. The Global Assessment Scale: a procedure for measuring overall severity of psychiatric disturbances. *Arch. Gen. Psychiatry.* 1976; 33:766–771. [PubMed: 938196]
- Erlenmeyer-Kimling L, Rock D, Roberts SA, et al. Attention, memory, and motor skills as childhood predictors of schizophrenia-related psychoses: the New York High-Risk Project. *Am. J. Psychiatry.* 2000; 157:1416–1422. [PubMed: 10964857]
- First, M.; Spitzer, RL.; Gibbon, M.; Williams, B.; Williams, JBW. *Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition*. New York, New York: Biometrics Research Department, New York State Psychiatric Institute; 1995.
- Fish B. Involvement of the central nervous system in infants with schizophrenia. *Arch. Neurol.* 1960; 2:115–121. [PubMed: 13823161]
- Fusar-Poli P, Bonoldi I, Yung AR, Borgwardt S, Kempton MJ, Valmaggia L, Barale F, Caverzasi E, McGuire P. Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. *Arch. Gen. Psychiatry.* 2012; 69(3):220–229. [PubMed: 22393215]
- Galvez-Buccollini J, Proal A, Tomaselli V, Trachtenberg M, Coconcea C, Chun J, Manschreck T, Fleming J, DeLisi L. Association between age at onset of psychosis and age at onset of cannabis use in non-affective psychosis. *Schizophr. Res.* 2012; 139(1–3):157–160. [PubMed: 22727454]

- GROUP. Evidence that familial liability for psychosis is expressed as differential sensitivity to cannabis: an analysis of patient–sibling and sibling–control pairs. *Arch. Gen. Psychiatry*. 2010; 68(2):138–147. [PubMed: 20921112]
- Harley M, Kelleher I, Clarke M, Lynch F, Arseneault L, Connor D, Fitzpatrick C, Cannon M. Cannabis use and childhood trauma interact additively to increase the risk of psychotic symptoms in adolescence. *Psychol. Med*. 2009;1–8. [PubMed: 19335938]
- Heins M, Simons C, Lataster T, Pfeifer S, Versmissen D, Lardinois M, Marcelis M, Delespaul P, Krabbendam L, van OsJ, Myin-Germeys I. for the GROUP project. Childhood trauma and psychosis: a case–control and case–sibling comparison across different levels of genetic liability, psychopathology, and type of trauma. *Am. J. Psychiatry*. 2011; 168(12):1286–1294. [PubMed: 21955935]
- Henquet C, Krabbendam L, Spauwen J, Kaplan C, Lieb R, Wittchen HU, van OsJ. Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. *BMJ*. 2005; 330:11. [PubMed: 15574485]
- Henquet C, Di FM, Morrison P, Kuepper R, Murray RM. Gene–environment interplay between cannabis and psychosis. *Schizophr. Bull*. 2008; 34:1111–1121. [PubMed: 18723841]
- Houston JE, Murphy J, Adamson G, Stringer M, Shevlin M. Childhood sexual abuse, early cannabis use, psychosis: testing an interaction model based on the national comorbidity survey. *Schizophr. Bull*. 2008; 34:580–585. [PubMed: 18024467]
- Janssen I, Hanssen M, Bak M, Bijl RV, de Graaf R, Vollebergh W, McKenzie K, van OsJ. Discrimination and delusional ideation. *Br. J. Psychiatry*. 2003; 182:71–76. [PubMed: 12509322]
- Janssen I, Krabbendam L, Bak M, Hanssen M, Vollebergh W, de Graaf R, van OsJ. Childhood abuse as a risk factor for psychotic experiences. *Acta Psychiatr. Scand*. 2004; 109:38–45. [PubMed: 14674957]
- Johnstone EC, Ebmeier KP, Miller P, Owens DG, Lawrie SM. Predicting schizophrenia: findings from the Edinburgh High-Risk Study. *Br. J. Psychiatry*. 2005; 186:18–25. [PubMed: 15630119]
- Karlsen S, Nazroo JY, McKenzie K, Bhui K, Weich S. Racism, psychosis and common mental disorder among ethnic minority groups in England. *Psychol. Med*. 2005; 35:1795–1803. [PubMed: 16194282]
- Kelly BD, O'Callaghan E, Waddington J, Feeney L, Browne S, Scully P, Clarke M, Quinn JF, McTigue O, Morgan MG, Kinsella A, Larkin C. Schizophrenia and the city: a review of the literature and prospective study of psychosis and urbanicity in Ireland. *Schizophr. Res*. 2010; 11(1):75–89. [PubMed: 19897342]
- Keshavan M, Montrose DM, Rajarethinam R, Diwadkar VA, Prasad KM, Sweeney JA. Psychopathology among offspring of parents with schizophrenia: relationship to premorbid impairments. *Schizophr. Res*. 2008; 103:114–120. [PubMed: 18442896]
- Konings M, Henquet C, Maharajh HD, Hutchinson G, van OJ. Early exposure to cannabis and risk for psychosis in young adolescents in Trinidad. *Acta Psychiatr. Scand*. 2008; 118:209–213. [PubMed: 18452569]
- Konings M, Stefanis N, Kuepper R, de Graaf R, ten Have M, van OsJ, Bakoula C, Henquet C. Replication in two independent population-based samples that childhood maltreatment and cannabis use synergistically impact on psychosis risk. *Psychol. Med*. 2012; 42(1):149–159. [PubMed: 21676285]
- Krabbendam L, van OsJ. Schizophrenia and urbanicity: a major environmental influence–conditional on genetic risk. *Schizophr. Bull*. 2005; 31:795–799. [PubMed: 16150958]
- Kuepper R, van OsJ, Lieb R, Wittchen HU, Henquet C. Do cannabis use and urbanicity co-participate in causing psychosis? Evidence from a 10-year follow-up cohort study. *Psychol. Med*. 2011; 41(10):2121–2129. [PubMed: 21466750]
- Matheson S, Shepard A, Laurens K, Carr V. A systematic meta-review grading the evidence for non-genetic risk factors and putative antecedents of schizophrenia. *Schizophr. Res*. 2011; 133:133–142. [PubMed: 21999904]
- Maxwell, ME. FIGS. Clinical Neurogenetics Branch, Intramural Research Program. Bethesda Maryland: NIMH; 1996.

- McGlashan, T.; Walsh, BC.; Woods, SW. The Psychosis Risk Syndrome: Handbook for Diagnosis and Follow-up. New York, New York: Oxford University Press; 2010.
- Mednick SA, Parnas J, Schulsinger F. The Copenhagen High-Risk Project, 1962–86. *Schizophr. Bull.* 1987; 13:485–495. [PubMed: 3629202]
- Miller B, Suvisaari J, Miettunen J, Jarvelin MR, Haukka J, Tanskanen A, Lonnqvist J, Isohannit M, Kirkpatrick B. Advanced paternal age and parental history of schizophrenia. *Schizophr. Res.* 2011; 133(1–3):125–132. [PubMed: 21937198]
- Mirsky AF, Silberman EK, Latz A, Nagler S. Adult outcomes of high-risk children: differential effects of town and kibbutz rearing. *Schizophr. Bull.* 1985; 11:150–154. [PubMed: 3983575]
- Nagler S, Marcus J, Sohlberg SC, Lifshitz M, Silberman EK. Clinical observation of high-risk children. *Schizophr. Bull.* 1985; 11:107–111. [PubMed: 3983569]
- Olivares J, Garcia_Lopez LJ, Hidalgo MD. The Social Phobia Scale and the Social Interaction Anxiety Scale: factor structure and reliability in a Spanish speaking population. *J. Psychoeduc. Assess.* 2001; 19:69–80.
- Reichenberg A, Weiser M, Caspi A, Knobler HY, Lubin G, Harvey PD, Rabinowitz J, Davidson M. Premorbid intellectual functioning and risk of schizophrenia and spectrum disorders. *J. Clin. Exp. Neuropsychol.* 2006; 28:193–207. [PubMed: 16484093]
- Scala S, Lasalvia A, Cristofalo D, Bonetto C, Ruggeri M. Neurocognitive profile and its association with psychopathology in first degree relatives of patients with schizophrenia. A case control study. *Psychiatry Res.* 2012; 200(2–3):137–143. [PubMed: 22652345]
- Stefanis NC, Delespaul P, Henquet C, Bakoula C, Stefanis CN, van OsJ. Early adolescent cannabis exposure and positive and negative dimensions of psychosis. *Addiction.* 2004; 99:1333–1341. [PubMed: 15369572]
- Tarbox SI, Pogue-Geile MF. Development of social functioning in preschizophrenia children and adolescents: a systematic review. *Psychol. Bull.* 2008; 134(4):561–583. [PubMed: 18605820]
- Torrey EF, Bartko JJ, Yolken RH. *Toxoplasma gondii* and other risk factors for schizophrenia: an update. *Schizophr. Bull.* 2012; 38(3):642–647. [PubMed: 22446566]
- van, OsJ; Pedersen, CB.; Mortensen, PB. Confirmation of synergy between urbanicity and familial liability in the causation of psychosis. *Am. J. Psychiatry.* 2004; 161:2312–2314. [PubMed: 15569906]
- van, OsJ; Rutten, BP.; Poulton, R. Gene–environment interactions in schizophrenia: review of epidemiological findings and future directions. *Schizophr. Bull.* 2008; 34:1066–1082. [PubMed: 18791076]
- Veling W, Susser E. Migration and psychotic disorders. *Expert. Rev. Neurother.* 2011; 11(1):65–75. [PubMed: 21158556]
- Wechsler, D. Wechsler Memory Scale Revised. New York: The Psychological Corporation; 1987.

Table 1

Demographic characteristics.

Variable	Healthy controls n = 25	FHR-non- CHR n = 25	FHR + CHR n = 25	Test statistic
	Mean (SD)			F value
Age	19.64 (5.23)	20.76 (5.85)	17.88 (3.24)	2.18
Years of education	12.44 (4.32)	12.00 (3.27)	11.04 (2.77)	1.01
	Number (%)			χ^2
Sex				
Male	10 (40.0%)	10 (40.0%)	12 (48.0%)	0.47
Female	15 (60%)	15 (60.0%)	13 (52.0%)	
Race				
Asian	3 (12.0%)	1 (4.0%)	1 (4.0%)	14.23
West/Central Asia/Middle East	0 (0.0%)	0 (0.0%)	2 (8.0%)	
White	22 (88.0%)	21 (84.0%)	19 (76.0%)	
Interracial	0 (0.0%)	3 (12.0%)	3 (12.0%)	
Marital status				
Single never married	24 (96.0%)	22 (88.0%)	24 (96.0%)	3.11
Married/Common law	0 (0.0%)	2 (8.0%)	1 (4.0%)	
Living with significant other	1 (4.0%)	1 (4.0%)	0 (0.0%)	
Currently working				
Yes, full time	6 (24.0%)	6 (24.0%)	1 (4.2%)	7.97
Yes, half time	3 (12.0%)	5 (20.0%)	7 (29.2%)	
No, have in last year	6 (24.0%)	6 (24.0%)	10 (41.7%)	
No, have not in last year	10 (40.0%)	8 (32.0%)	6 (25.0%)	
Currently enrolled as a student	22 (88.0%)	19 (76.0%)	20 (83.3%)	1.26

Table 2

Group comparisons of risk factors.

Variable	Healthy controls n = 25	FHR-non-CHR n = 25	FHR + CHR n = 25	Test statistic
	Number (%)			X ²
Immigration status				
Born in Canada	21 (84.0%)	24 (96.0%)	21 (88.0%)	7.21
1st Generation Migrant	3 (12.0%)	1 (4.0%)	0 (0.0%)	
2nd Generation Migrant	1 (4.0%)	0 (0.0%)	3 (12.0%)	
Trauma				
Psychological bullying	10 (40.0%)	14 (56.0%)	18 (75.0%) ^a	6.12 [*]
Physical bullying	5 (20.0%)	8 (32.0%)	8 (33.3%)	1.32
Emotional Neglect	3 (12.0%)	10 (40.0%) ^a	13 (54.2%) ^a	9.95 ^{**}
Psychological Abuse	2 (8.0%)	11 (44.0%) ^a	12 (50.0%) ^a	11.42 [*]
Physical Abuse	3 (12.0%)	9 (36.0%)	8 (33.3%)	4.37
Sexual Abuse	0 (0.0%)	4 (16.0%)	5 (20.8%)	5.5
			Mean (SD)	X ²
Total bullying	0.60 (0.76)	0.88 (0.72)	1.08 (0.72)	5.47 ^{***}
Total trauma	0.84 (1.25)	2.24 (1.79) ^a	2.67 (1.76) ^a	17.68 ^{****}
	Number (%)			X ²
Head injury				
Ever had a head injury: Yes	7 (28.0%)	10 (40.0%)	15 (62.5%) ^a	6.10 [*]
	Mean (SD)			F value
Lifetime # of head injuries	1.00 (0.94)	2.40 (2.76)	1.60 (0.74)	1.88
	Number (%)			X ²
Cannabis				
Ever smoked: Yes	9 (36.0%)	13 (52.0%)	16 (69.6%)	5.41
	Mean (SD)			X ²
Current level of use	1.00 (0.00)	1.16 (0.37) ^a	1.39 (0.66) ^a	8.79 [*]
Frequency of use in last month	0.00 (0.00)	0.28 (0.74) ^a	1.13 (1.94) ^a	9.12 [*]
				F value
# Times smoked cannabis	72.00 (107.01)	89.77 (115.60)	123.19 (132.82)	0.57
Age first tried cannabis	15.56 (2.19)	15.67 (1.67) ^b	13.94 (1.83)	3.65 [*]
IQ				
WASI IQ score	107.84 (12.20)	110.00 (12.25) ^b	100.71 (12.65)	3.32 [*]
Perceived discrimination				
Last year	0.24 (0.83)	1.20 (1.35) ^a	1.70 (1.58) ^a	8.04 ^{**}

Variable	Healthy controls n = 25	FHR-non-CHR n = 25	FHR + CHR n = 25	Test statistic
	Number (%)			χ^2
Lifetime	0.84 (1.41)	1.80 (2.06)	2.57 (1.88) ^a	5.54 ^{**}

Trauma: Range 0–6 (0 = no traumas). Cannabis: Current Level: 1 = abstinent, 2 = use without impairment, 3 = abuse, 4 = dependence, 5 = dependence with institutionalization. Cannabis: Frequency: 0 = no use, 1 = 1–2 in past month, 2 = 3–4 in past month, 3 = 1–2 per week, 4 = 3–4 per week, 5 = almost daily. Perceived Discrimination: Range 0–9 (0 = no perceived discrimination).

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

**** $p < 0.0001$.

^aSignificantly different from controls.

^bSignificantly different from FHR + CHR.

Table 3

Group comparisons of psychopathology & functioning.

Variable	Healthy controls N = 25	FHR-non-CHR N = 25	FHR + CHR N = 25	Test statistic
	Mean (SD)			F value
Depression				
CDSS	0.28 (0.74)	2.76 (3.81) ^a	4.71 (4.35) ^a	11.83 ^{****}
Anxiety				
SIAS	7.08 (5.83)	18.76 (15.84) ^a	27.63 (17.13) ^a	13.57 ^{****}
SAS	23.88 (3.45)	30.24 (13.24) ^b	37.71 (10.47) ^a	11.79 ^{***}
GAF	87.92 (4.40)	80.44 (11.93) ^{a,b}	45.75 (13.85) ^a	117.04 ^{**}
Social functioning	9.13 (0.99)	8.12 (1.36) ^{a,b}	6.70 (1.46) ^a	19.74 ^{****}
Role functioning	9.00 (1.06)	8.00 (2.02) ^b	5.65 (2.42) ^a	17.71 ^{****}
Premorbid functioning				
Childhood	0.13 (0.17)	0.16 (0.13)	0.25 (0.15) ^a	3.67 [*]
Early adolescence	0.08 (0.10)	0.23 (0.15) ^a	0.27 (0.13) ^a	13.59 ^{****}
Late	0.06 (0.06)	0.23 (0.14) ^a	0.33 (0.15) ^a	18.10 ^{****}
Adolescence				

GAF = Global Assessment of Functioning.

* p < 0.05.

** p < 0.01.

*** p < 0.001.

**** p < 0.0001.

^aSignificantly different from controls.^bSignificantly different from FHR + CHR.

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Table 4

Logistic Regression — Predictors of Psychosis Risk Syndrome.

Outcome Variable	OR	B	SE	Wald	df	95% CI	p
Age first tried cannabis	0.44	−0.82	0.42	3.82	1	0.195–1.003	0.05
WASI IQ	1.00	0.02	0.048	0.02	1	0.912–1.102	0.96