Delineating factors associated with vulnerability to psychosis in young people

by

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Abstract

Introduction: The etiology of psychosis is complex and appears to be the result of the confluence of several predisposing influences, such as obstetric complications, prenatal life events, life adversity and/or trauma and substance use, in particular cannabis use, operating on top of genetic risk. We sought to assess a group of local adolescents to see if their experience of these predisposing influences might predict their scores on scales of psychosis proneness.

Methods: Participants were high school students from Edmonton and the surrounding area (n = 221). Psychosis proneness was assessed using the Magical Ideation Scale (MIS), a measure of positive schizotypy, and the Social Anhedonia Scale (SAS), a measure of negative schizotypy. Predisposing factors were assessed by a measure of adverse events (AEs) and a questionnaire on cannabis use. In addition, 73 participants agreed to have their mothers complete a questionnaire regarding obstetric complications (OCs) and prenatal life events or maternal stressors (PNMS).

Results: AEs were common, with 91% endorsing at least one and 69% endorsing multiple events. AEs were associated with scores on the MIS (standardized $\beta = 0.32$, $p < 0.001$), but not on the SAS. Fifty-four percent of mothers endorsed at least one OC and 59% endorsed at least one PNMS. No association was found between OCs or PNMS and MIS or SAS score. Thirty-four percent of participants endorsed cannabis use at least once in their lifetime, and 17% endorsed having used in the past 30 days. Cannabis use at least once in lifetime was associated with MIS score (standardized $\beta = 0.18$, $p = 0.006$), but not with SAS score. AEs were also associated with cannabis use

(standardized $\beta = 0.26$, $p < 0.001$). In combining predisposing factors to attempt to augment the association, AEs combined with PNMS resulted in an adjusted R^2 of 0.12 for an association with MIS, an increase over the adjusted R^2 for AEs alone ($R^2 = 0.10$). Similarly, when AEs were combined with OCs, the adjusted R^2 was 0.12 for association with MIS.

Discussion: AEs and cannabis use were highly associated with scores on the MIS, linking positive schizotypy to life adversity and cannabis use, as anticipated. However, AEs were also associated with cannabis use, suggesting perhaps the cannabis link is mediated by AEs. However, it is important to note both associations as both have individually been linked to psychosis, particularly when cannabis use is begun earlier in life. As the evidence for a link of OCs and PNMS with psychosis is strong, the lack of results here was unanticipated. However, when added to AEs, they improved the predictive model for MIS score, and therefore may be acting as additional life stressors. No risk factor was found to be associated with SAS. It is possible that the MIS is more sensitive to environmental influences of psychosis proneness, whereas the SAS might be more sensitive to a genetic predisposition. Of note, AEs were very highly endorsed in this study compared to global and recent local analyses. This may indicate a problem with data collection in our study, over-endorsement by the participants, or possibly an indication that other measures are not capturing full endorsement in their assessments. Further research should consider the associations of each of these risk factors and how interactions are affecting the proneness model. Biological and psychological mechanisms whereby these vulnerabilities affect proneness should be considered.

Preface

This thesis is an original work by Leslie J. Roper. The research project, of which this thesis is a part, received ethics approval from the University of Alberta Research Ethics Board, Project Name “Improving outcomes in first episode schizophrenia”, P.I.: Dr. Scot E. Purdon, No. Pro00003635, October 14, 2008, and Project Name “Improving outcomes in first episode schizophrenia: an education and genetic focused approach”, P.I.: Dr. Scot E. Purdon, No. Pro00002414, March 25, 2009.

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List of Abbreviations

AADAC	Alberta Alcohol and Drug Abuse Commission
AADAC-RDS	Alberta Alcohol and Drug Abuse Commission Recent Drug Survey
ACE	Adverse Childhood Experiences
AE	Adverse Experiences
AMHRL	Addiction and Mental Health Research Laboratory of the University of Alberta
ANOVA	Analysis of Variance
β	Beta
C-section	Caesarean section
CALM	Career and Life Management course
COMT	Catechol-O-Methyltransferase
CPPS	Chapman Psychosis Proneness Scales
CTQ	Childhood Trauma Questionnaire
df	Degrees of freedom
DSM-5	Diagnostic and Statistical Manual of Mental Disorders - 5th Edition
DSM-IV TR	Diagnostic and Statistical Manual of Mental Disorders - 4th Edition Revised
GWAS	Genome-wide associations studies
HPA	Hypothalamic-Pituitary-Adrenal
HR	High-Risk
HREB	Human Research Ethics Board
ICD-10	International Classification of Diseases - 10th Revision
MIS	Magical Ideation Scale

OC	Obstetric Complications
OR	Odds Ratio
p-values	Significance of the statistical test
PAS	Physical Anhedonia Scale
PerAb	Perceptual Aberration Scale
PLE	Psychotic-like experiences
PNMS	Prenatal Maternal Stressors
r	Pearson's correlation coefficient (parametric)
R^2	Measure of variance
ρ	Spearman's rho correlation coefficient (non-parametric)
SAS	Social Anhedonia Scale
SD	Standard Deviation
SES	Social Economic Status
Std	Standardized

1.0 Introduction

Psychosis is characterized by a highly variable set of experiences whereby perceptions, behaviours and cognitions are distorted, and manifest in delusions, hallucinations, thought disorder, or a mixture thereof (Butcher et al., 2004). Most commonly, onset of psychosis occurs in late adolescence, and while an episode may be brief and singular, the experiences may also persist across the lifespan (Butcher et al., 2004).

1.1 Continuum of psychosis

In clinical terms, the psychosis phenotype is dichotomous; a person either has a psychotic disorder identified by specific criterion as determined by psychiatric classification systems (i.e. DSM-5 and ICD-10), or he/she does not. However, from an epidemiological standpoint, psychotic experiences in the general population appear to lie on a continuum, and cannot be assessed based only on an all-or-none set of criteria (Johns and van Os, 2001; Rose and Barker, 1978). The psychosis continuum ranges from relatively mild abnormal perceptions and idiosyncratic beliefs, through psychotic-like experiences (PLEs), also known as sub-clinical experiences, and attenuated psychosis, to more significant symptoms for which duration extends beyond a day, a month or six months, meeting criteria for a brief psychotic disorder, a schizophreniform disorder, or schizophrenia, respectively (American Psychiatric Association, 2013). PLEs are common in the general population with a reported prevalence around 5.3% (van Os et al., 2009), and appear to be even more prevalent in children (Linscott and van Os, 2013). PLEs may be rare and/or easily dismissed by the individual; however, as the severity and/or frequency of these experiences rise, the individual would be placed

further along in the continuum to a psychotic disorder and towards a chronic psychotic illness and schizophrenia (van Os et al., 2009).

In 1962, Paul E. Meehl proposed a comprehensive model for the etiology of schizophrenia that has continued to influence the field, likely more than has been realized (Meehl, 1962). Before Meehl, Sandor Rado suggested there might be a schizophrenic phenotype (schizotype) whereby an afflicted person is handicapped neurodevelopmentally, and thus they must use compensatory mechanisms that present as schizotypal personality traits and behaviour (Rado, 1953). Building on this idea, Meehl introduced a model of schizophrenia around the idea of schizotaxia. Schizotaxia is postulated as being the result of having a "schizogene" where a person's neurodevelopment is directly related to the presence or absence of this particular gene. If the gene is "turned on", it results in abnormal synaptic transmission, described as "*hypokrisia*" or an "insufficiency of separation, differentiation, or discrimination" at a neuronal level. Meehl described this as "cognitive slippage", the basis for all psychotic symptomatology (e.g. affective and cognitive irregularities, loosening of associations, etc.). From this, Meehl suggested that the schizotaxic brain becomes vulnerable to other factors, such as social learning interactions and other genetic factors he termed "*polygenic potentiators*". He stressed that, while it is possible for a schizotaxic (genetically predisposed) person to display no psychotic symptomatology at all, it would only be due to a perfect upbringing with zero negative exposure to any polygenic potentiators, deemed a very unlikely scenario. Most (if not all) people with a schizotaxic brain will display some psychotic symptomatology, or "*schizotypy*", with severity being related to a mixture of various life experiences, exposures and epigenetic influences

(Lenzenweger, 2006a). While it is now known that no single gene is indicative of risk for schizotypy or future onset of schizophrenia, Meehl's theory is still compatible with a polygenic model (Lenzenweger, 2015). This is the basis for the way we presently consider the etiology of psychosis and schizophrenia, as well as underlying the general premise for the psychotic continuum.

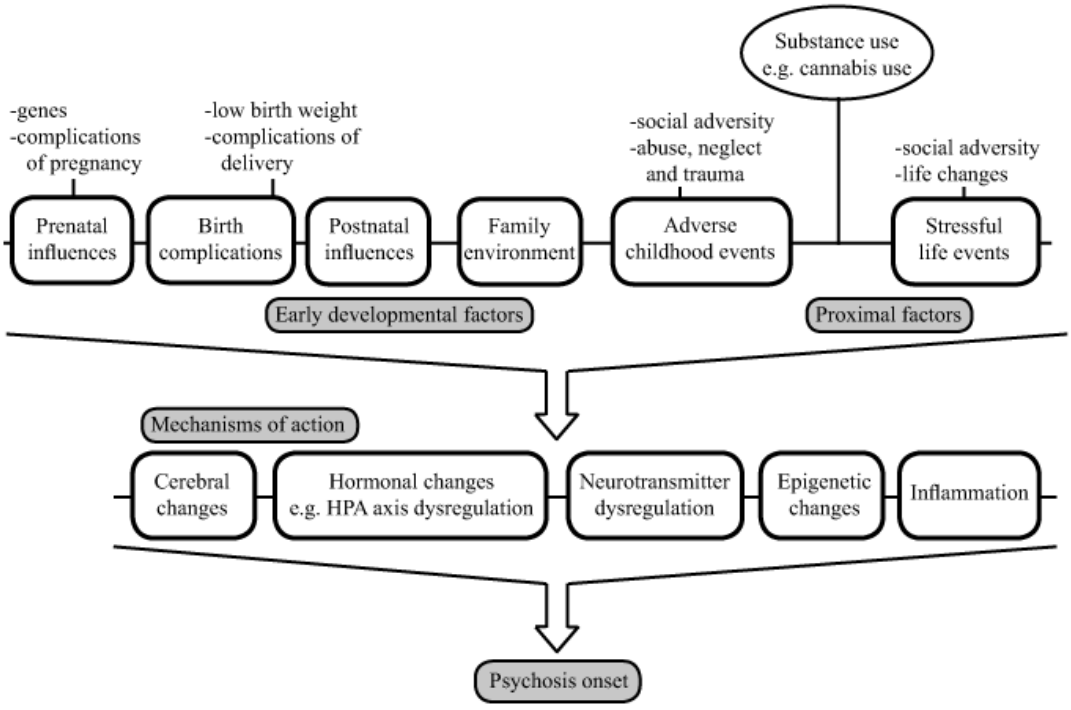
A prevalent area of research is related to those on the continuum who might be considered at high-risk (HR), or prodromal, for a psychotic break or onset of a schizophrenic illness. Early interventions for individuals with psychosis result in a better prognosis, and some have shown that proper and timely treatment of a prodromal individual may even prevent transition to psychosis (Yung et al., 2007; Yung et al., 2011). The difficulty here is the low incidence of transition, even in an HR population (Fusar-Poli et al., 2012). Much research has focused on refining methods whereby HR participants might be determined. Currently HR individuals are determined by criteria in one of these categories: an assessment of basic symptoms, genetic/familial risk, presence of transient or intermittent psychotic episodes, or subthreshold/attenuated symptoms of psychosis (Fusar-Poli et al., 2013). Several measures have been created to quantify risk, including assessments of schizotypy, as well as clinical assessments of risk and symptomatology (Chapman and Chapman, 1980; Fusar-Poli et al., 2013; Kwapil and Barrantes-Vidal, 2015).

1.2 Vulnerability to psychosis

While many factors appear to play a role in vulnerability to psychosis, exposure to any single predisposing factor on its own is unlikely to lead to onset of a psychotic episode.

Indeed, the etiology of psychosis consists of a complex integration of several risk factors and life experiences (Figure 1). While there have been many theories over the years, a leading current model suggests that a synergistic effect of genetic predisposition, environmental influences, and gene-environment interactions all contribute to the genesis of a psychotic illness (Jaffee and Price, 2008; Lataster et al., 2012; van Nierop et al., 2013).

Figure 1. The complex etiology of the onset of psychosis.



1.2.1 Genetic predisposition

Genetic predisposition is clearly associated with psychosis (McGuffin et al., 1984). Currently accepted heritability estimates are around 50 – 80% and some studies claim even higher estimates (Cardno et al., 1999; Cardno et al., 2002; Gottesman and Shields, 1967). However, recent studies indicate that heritability may have been overestimated due to inherent biases in sample ascertainment and methodology in the earlier studies. When looking exclusively at phenotypic traits of psychosis, and not just in families with high rates of psychosis, heritability estimates were approximately 31% within the nuclear family and 44% including extended family (Light et al., 2014). Regardless, genetic vulnerability cannot alone account for all psychotic illness. Environmental influences and epigenetics, the latter being the way environment and life experiences may influence and change our gene expression, may exert significant influence as well (Read et al., 2009).

Over the years a great amount of research has been undertaken to identify and locate possible genes of vulnerability. More recently, genome-wide association studies (GWAS) have identified statistically significant genetic markers associated with schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics, 2014). Results from GWAS should be beneficial for more focused research into the etiology and continuum of psychosis and schizophrenia, and how these genes may be affected by environmental influences. Of note, this work has implicated several relevant markers across the genome, not a single schizogene, as suggested by Meehl. The Meehl theory remains sound, however, if you consider the schizogene to be the base genetic risk attributable to several genetic markers, whereupon environmental and epigenetic

factors may or may not act (Lenzenweger, 2015). In addition, GWAS analyses provide polygenic risk scores that future studies may be able to use to better examine gene-environment interactions (Schizophrenia Working Group of the Psychiatric Genomics, 2014; van Winkel and Kuepper, 2014).

1.2.2 Prenatal influences and obstetric complications

Prenatal and obstetric complications (OCs) have long been linked to later psychological health of the offspring. To name a few, low birth weight, maternal diabetes, older paternal age, winter birth, maternal infections, prenatal maternal nutrition and Prenatal Maternal Stressors (PNMS) have all been associated with schizophrenia (Boog, 2004; Brown, 2011; King and Laplante, 2005; Kirkbride et al., 2012; Machon et al., 1987; Mednick et al., 1994; Rifkin et al., 1993). Additionally, an excess of birth complications has been observed in the histories of individuals at high risk for developing schizophrenia (Ichiki et al., 2000; Lewis and Murray, 1987; Mednick et al., 1994).

Cannon, Jones & Murray (2002) suggest three major categories of OCs: 1) complications during pregnancy such as diabetes, preeclampsia (hypertension), and bleeding, 2) abnormal fetal growth and development such as low birth weight and 3) complications of delivery such as emergency Caesarean section (C-section), asphyxia and uterine atony (Cannon et al., 2002). The mechanism whereby these circumstances may result in poor mental health outcomes is not entirely understood. However, for complications of pregnancy, hypoxia is an oft suggested cause for later mental health problems. This is particularly true for those whose mothers experienced preeclampsia and prenatal bleeding (King et al., 2010). Low birth weight appears to be strikingly

linked to schizophrenia with the Cannon et al. meta-analysis (2002) suggesting a 4 fold increased risk; however, as low birth weight is often related to other adverse influences during gestation, this may not be a direct association.

PNMS have received increasing attention in the last 15 years, and there is compelling evidence both in animal and human studies that PNMS have a significant effect on psychological risk (Beydoun and Saftlas, 2008). Although the mechanism of PNMS effects on psychological risk has yet to be articulated, alterations in hormonal response (e.g. cortisol surge) may be relevant to neurodevelopmental changes in the brain of the unborn child. To complicate the matter further, there is support for both an indirect and direct influence of PNMS, either exerting an effect on development or contributing to a later obstetric complication (Beydoun and Saftlas, 2008; King et al., 2010).

It is difficult to determine how PNMS might have an effect on the health outcomes of the offspring. This is partly because no one stressor is created equal for all individuals. Several factors are at play in the maternal stress response such as 1) the objective amount of exposure to a stressor, 2) the subjective level of distress, 3) the physiological response to the stressor, and 4) the individual's psychological and social circumstances, such as relative coping skills, support system and personality traits (King et al., 2010). All of these factors may mitigate or amplify the effect of stressors on an individual basis but it is also reasonable to assume a contribution to increased risk from the additive or multiplicative effects of these stressors.

1.2.3 Adverse life events

Traumatic and/or stressful life experiences have great impact on many facets of physical and mental health (Felitti et al., 1998; Holmes and Rahe, 1967; Salleh, 2008). Adverse life events are also highly associated with mental health concerns including substance use (Andersen and Teicher, 2009), social anxiety disorder (Brook and Schmidt, 2008), addictive behaviours (Lee et al., 2012), and suicidality (Pompili et al., 2011), as well as psychosis and schizophrenia (Lataster et al., 2012; Van Os et al., 2014; van Winkel et al., 2013). While stress in life is fairly commonplace, how each individual reacts to, experiences, and resolves this stress is not universal. Moreover, particularly stressful or traumatic life events, and/or an abundance of stressful life events may have implications for later health (Anda et al., 2006; Brugha and Conroy, 1985; Dube et al., 2003b; Holmes and Rahe, 1967).

1.2.3.1 Childhood adversity

Adversity in childhood has long-lasting negative consequences into adulthood, affecting general health and well-being (Anda et al., 2006; Dube et al., 2003b; Felitti et al., 1998). Some studies estimate that approximately 40% of the general population over the world have experienced childhood adversity (Kessler et al., 2010). Moreover, having experienced at least one ACE increases the risk for more ACEs (Dong et al., 2004). In addition, the number of ACEs experienced appears to have an additive effect later in life: the more ACEs experienced, the greater the risk for social and health issues later in life (Anda et al., 2006; Felitti et al., 1998).

Childhood adversity has been linked specifically to onset of psychosis later in life. A recent investigation reported that all transitions to psychosis in their sample were associated with at least some exposure to environmental risk factors, with the greatest risk by far being related to having experienced childhood trauma (OR = 34.4) (van Nierop et al., 2013). Another meta-analysis showed strong associations (odds ratio (OR) = 2.78) between ACEs and emergent psychosis in patient-control, prospective cohort and cross-sectional cohort study designs. In case-control study analyses only, individuals who had experienced psychosis were 2.72 times more likely to have experienced childhood adversities than controls, and the estimated attributable risk of ACEs contributing to psychosis later in life was 33% (Varese et al., 2012).

Childhood trauma has also been associated with psychosis in a dose-response fashion, with the likelihood of psychosis increasing with the number of traumatic events (Heins et al., 2011). Patients had an OR of 4.53, and siblings of patients had an OR of 1.61 of having experienced trauma compared to controls. However, patients had an OR of 2.60 when compared to their siblings, indicating perhaps that patients have experienced more trauma than their siblings (Heins et al., 2011). Moreover, in a comparison of patients with psychosis who had experienced trauma in childhood to those who had not, those who had traumatic experiences showed a significant excess of hallucinations and delusions in terms of types of psychotic symptoms, particularly when there was a history of sexual assault (Hainsworth et al., 2011).

1.2.3.2 Adversity later in life

Life stressors have also been implicated as a precipitating factor for a psychotic episode. It is important to determine how and when a stressful event may trigger a psychotic event. One study assessed the timing, independence, threat and intrusiveness of stressful events over the year prior to onset of a psychotic episode and found that adverse events were considered more stressful and intrusive in the three months prior to onset of the psychotic event, despite reporting frequent adverse events for the entire preceding year (Raune et al., 2009). Also, a greater number of adverse life events were reported in the three months preceding the onset of psychosis compared to a healthy sample group from the general population in data collected over 6 months (Bebbington et al., 1993). Interestingly, the period of relevance for adverse events appears to be shorter for psychosis than for depression, where life events in the six to nine months prior to onset have been associated with the illness (Brugha and Conroy, 1985; Keers et al., 2011; Uher et al., 2011). Of note, stressful life events in the preceding four weeks have been associated with psychotic relapses (Fallon, 2009).

Adversity later in life may also work synergistically with early life trauma to lead to onset of psychosis (Roper et al., 2015). Adversity early in life is associated with an excess of later life stressors, and it appears that childhood adversity may either increase likelihood of exposure to later life stressors, or it may make an individual more vulnerable to the effects of later adversity (Lataster et al., 2012) (18). Biological mechanisms, such as effects on the hypothalamic-pituitary-adrenal axis (HPA), have been suggested as a means whereby epigenetic changes caused by childhood traumatic experiences and exposures may prime an individual to be at a greater

sensitivity to stressors later in life (Elzinga et al., 2008; Holtzman et al., 2012; McCrory et al., 2012).

1.2.3.3 Life adversity and symptomatology

It has been suggested that particular stressful life events may be reflected in the core psychotic themes and symptoms in a psychotic illness, although research in this area has been inconclusive to date. Establishing a psychological pathway whereby life experiences might specifically affect a psychotic illness would not only be a huge step towards greater understanding of the complex etiology, but also could be very useful for treatment and prevention strategies (Beards and Fisher, 2014; Bentall, 2014; Raune et al., 2006).

Several studies have attempted to link childhood adversity to specific symptoms in later psychotic presentation. There is general agreement that childhood sexual abuse is associated with positive symptoms of psychosis and auditory hallucinations in particular (Bentall et al., 2014; Bentall et al., 2012; Ucok and Bikmaz, 2007). Furthermore, childhood rape has been associated specifically with hallucinations when contributions from paranoia were removed (Bentall et al., 2012). Positive symptoms were also associated with child abuse of any kind, but not with neglect (Heins et al., 2011). Links have also been drawn between paranoia and the trauma associated with institutional care, and between both positive and negative symptoms and physical abuse (Bentall et al., 2012). However, these studies also found that exposure to more than one adversity in childhood increased the risk of psychosis in general, without specificity with regard to symptomatology (Bentall et al., 2012), and indeed, a recent study has similarly

suggested as much, although life events related to intention-to-harm may be of some significance (van Nierop et al., 2014).

Research into the effects of later life adversity and specific links to symptomatology has been a relatively overlooked area (Beards and Fisher, 2014). However, intrusive life events in particular have been associated with the development of persecutory delusional thoughts, and life events involving loss have been negatively associated with grandiose delusions (Raune et al., 2006). Additionally, depressive delusions have been associated with having life experiences of a dangerous nature (Raune et al., 2006). It has also been suggested that recent life events play a role in mediating the development of psychotic symptoms following childhood adversity, and that both may work synergistically to result in specific symptomatology (Beards and Fisher, 2014; Morgan et al., 2014).

While most earlier studies have attempted to find associations between a category of trauma and later specific symptomatology, current research has been geared toward identifying a mechanism or pathway whereby the adverse life event may influence the presentation of a psychotic illness (Beards and Fisher, 2014; Bentall et al., 2014). A review of this area recently considered both the biological mechanisms that stressful life events may contribute to the presentation of psychosis, as well as the psychological pathways whereby specific forms of childhood adversity may affect emergent psychosis symptoms (Bentall et al., 2014).

1.2.4 Cannabis use

There is general agreement that cannabis use is a risk factor for psychosis, but as with other suggested vulnerabilities, cannabis alone is not sufficient to lead to psychosis, and most people who use cannabis will not develop a psychotic illness. Nonetheless, there have been strong associations between earlier use of cannabis in adolescence, potency of the drug, as well as genetic and epigenetic influences with future onset of psychosis (van Winkel and Kuepper, 2014).

Several studies have noted an effect of age of first use of cannabis and increased risk of psychosis later in life. For example, cannabis use on or before the age of 15 resulted in a 4 times greater likelihood of later diagnosis of a schizophreniform illness at the age of 26 than in controls (Arseneault et al., 2002). Moreover, cannabis use before the age of 16 demonstrated stronger associations with both positive and negative symptomatology of later psychosis than cannabis use later in life, regardless of frequency of use (Stefanis et al., 2004). Recent studies have corroborated this effect, finding that use before the age of 16 was associated with an increased risk of psychosis (Di Forti et al., 2014; Schubart et al., 2011; Stowkowy and Addington, 2013).

Several studies have pointed to specific genetic markers and their effects on risk of future psychosis following cannabis use. Cannabis use and later psychosis onset was linked to a subset of the population with a specific polymorphism in the catechol-O-methyltransferase (*COMT*) gene, although replication of this finding has been mixed (Caspi et al., 2005; Decoster et al., 2012). *AKT1* is another gene that has shown promise, with carriers of a specific variation of the rs2494732 single nucleotide

polymorphism showing an increase in risk of later psychosis following cannabis use (Di Forti et al., 2012; van Winkel et al., 2011).

Cannabis use has also been associated with younger age of onset of psychosis (Large et al., 2011). In addition, preliminary analysis indicates an effect of the *COMT* Val158Met polymorphism on age of onset of substance-induced psychosis (Aitchison et al., 2014). Moreover, it has become important to consider the potency of cannabis available and its effects on emergent psychosis. High-potency cannabis use appears to increase likelihood of future psychosis when compared to lower-potency cannabis use (Di Forti et al., 2009; Di Forti et al., 2014).

Other suggested vulnerabilities to psychosis may also interact with cannabis use to increase risk of later psychosis. For example, cannabis use may interact with urbanicity to increase likelihood of later psychosis (Kuepper et al., 2011b). In addition, several studies have suggested that individuals with traumatic experiences earlier in their life were at greater risk of later psychosis following cannabis use than individuals who reported no trauma (Harley et al., 2010; Houston et al., 2008; Houston et al., 2011; Konings et al., 2012). On the other hand, this has not been found universally, and needs further investigation (Kuepper et al., 2011a).

Although a causal effect between cannabis use and later onset of psychosis appears probable, there is evidence that those at risk for psychosis are perhaps more likely to turn to cannabis as a type of self-medication, or that those at genetic risk for psychosis are also at risk for cannabis use, where cannabis use and psychosis themselves are unrelated. However, overall studies suggesting a self-medication or

genetic confounding of the causal effect have been inconsistent, while evidence for a causal temporal link between cannabis use and future psychosis has been robust and consistent (van Winkel and Kuepper, 2014).

1.2.5 Other vulnerabilities

Social disadvantage, such as minority status, urban birth/upbringing and neighborhood deprivation, including experiences of incidents of crime, poor education opportunities and poor employment availability, have all been linked to psychosis (Bhavsar et al., 2014; Kelly et al., 2010; Spauwen et al., 2004; van Nierop et al., 2013; van Os et al., 2010). A recent study concluded that transition to psychosis is virtually always associated with some form of environmental influence operating on background genetic risk, including urban birth with an odds ratio of 3.7, and membership in a minority ethnic group with an odds ratio of 3.8 (van Nierop et al., 2013). These environmental influences may act as further stressors in a complex etiological model of psychosis. One could argue that these environmental influences act as additional life stressors and adversities, and therefore may interact with the etiological model of psychosis in a similar manner as adverse life events (van Os et al., 2010).

1.3 Relevant features of a predisposition to psychosis

As previously mentioned, attempts to identify individuals at greater risk for psychosis is a fervent area of study. Meehl's concept of schizotypy, or the level of expression of psychotic symptomatology resulting from environmental, epigenetic and individual/personality influences on an underlying genetic vulnerability, has shown great utility as the basis and framework for the psychosis continuum (Lenzenweger, 2006b,

2015). Indicators of schizotypy are widely used to attempt to determine those who may be at risk, from laboratory measures and psychometric assessments to clinical and diagnostic measures, such as the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) (Lenzenweger, 2015). While the DSM-5 ultimately results in a dichotomous diagnosis of psychotic disorder or not, the concept of schizotypy and the psychosis continuum has helped to shift the margins of this narrow schizophrenia phenotype (Lenzenweger, 2015), now including at least consideration of an attenuated psychosis syndrome, as well as regarding schizotypal pathology as an indicator of schizophrenia spectrum disorder (American Psychiatric Association, 2013).

One group out of Wisconsin created several narrowly focused measures of the diverse and variable symptoms of psychosis proneness, or schizotypy as proposed by Meehl, dubbed the Chapman Psychosis Proneness Scales (CPPS) (Chapman and Chapman, 1979). The group began with measures of perceptual aberrations (PerAb) and physical anhedonia (PAS), followed by the Magical Ideation Scale (MIS), the Social Anhedonia Scale (SAS) and a scale of impulse control (Chapman et al., 1976; Chapman et al., 1980; Eckblad and Chapman, 1983). Of these, the MIS, PerAb and SAS (also known as the Revised SAS, or R-SAS, in the literature following an update by the group in 1982) have been widely used and validated over time as useful tools in the quest to identify a psychological predisposition to psychosis (Chapman et al., 1994; Eckblad et al., 1982; Gooding et al., 2005b; Kwapil et al., 2012; Kwapil et al., 2013). These measures of schizotypy may be instrumental in offering an intermediate, heritable, state-independent component of the psychosis phenotype.

1.3.1 Schizotypal ideation

Abnormal perceptions, delusional ideas and eccentric behaviour are hallmark signs of schizotypal ideation. Severity of schizotypal ideation may be key to predicting an individual's risk of developing psychosis, and to quantify this risk, the MIS was introduced (Eckblad and Chapman, 1983).

Using MIS scores as a marker for schizophrenia-spectrum psychosis does in fact show mixed results. An association between MIS score and schizophrenia is evident in that individuals with schizophrenia have elevated MIS scores compared to healthy controls, and this effect appears to remain over time and through variability of active symptoms. Despite this clear association, the MIS score is still closely linked to active symptoms of psychosis and undoubtedly covaries with active symptoms of psychosis. As clinical symptoms are resolved, scores on the MIS also decrease, suggesting that the MIS may better quantify active symptoms of psychopathology rather than an underlying trait, and therefore there is relatively weak evidence that using the MIS will help predict emergent psychosis predisposition. Moreover, the CPPS group reported the strongest evidence for the predictive power of the MIS in a longitudinal study that followed a large group (n=508) over 10 years to determine those at risk for psychosis based on scores from the MIS as well as another scale of schizotypy, the Perceptual Aberration Scale (PerAb), thus confounding the predictive power of the MIS alone (Chapman et al., 1994). However, several studies have continued to support the viability of the MIS for psychosis proneness with high alpha coefficients of 0.82-0.84 indicating strong scale reliability (Brambilla et al., 2014; Kwapil et al., 2013), and longitudinal

studies that have found individuals with high MIS scores have a greater likelihood of psychosis later in life (Gooding et al., 2005b; Kwapil et al., 2013).

In addition, the MIS persists as a viable indicator of psychopathology due to its link to several neuropsychological markers and putative endophenotypes of schizophrenia-spectrum psychosis. Unmedicated or minimally medicated individuals with schizophrenia and individuals considered at high risk for psychosis as determined by MIS scores seem to exhibit the same relative left hemisphere disadvantage as noted across several neuropsychological assessments such as visual field neglect (Brugger and Graves, 1997), hand force persistence (Purdon et al., 2001), and olfactory acuity (Purdon and Flor-Henry, 2000), among others. In addition, a recent study used the MIS as a measure of psychosis proneness and found marked associations with personality traits associated with schizotypy (such as poor cooperativeness and self-directedness) and that there may be shared genetic and environmental effects between magical ideation and personality traits (Brambilla et al., 2014).

1.3.2 Anhedonia

Anhedonia has long been a prominent symptom for mood disorders, especially depression, and indeed early writings note the inability to derive pleasure as an integral part of the illness of schizophrenia (Bleuler, 1950; Kraepelin, 1919). Additionally, anhedonia has been suggested as a relevant symptom of proneness to psychosis and schizotypy (Meehl, 1962). Despite these early observations, it is only more recently that its importance to the onset and course of psychosis and schizophrenia has gained popularity (Wolf, 2006).

Two types of anhedonia have been identified: social anhedonia (inability to experience pleasure from social interactions and relationships) and physical anhedonia (inability to experience pleasure from sensory experiences). In general, social anhedonia is more closely related to negative symptomatology seen in schizophrenia than physical anhedonia (Loas et al., 2009); however physical anhedonia is highly correlated with many aspects of quality of life (Ritsner et al., 2011). The CPPS include measures of both social and physical anhedonia, and both have their merits, measure similar constructs and measuring both can bolster ratings of negative symptomatology (Chapman et al., 1994; Chapman et al., 1976; Kwapil et al., 2013). However, despite being often relegated solely to a measure of negative symptomatology, social anhedonia has also been associated with positive symptoms of psychosis and therefore may be a robust proneness measure (Fonseca-Pedrero et al., 2010).

Scores on the SAS alone have proven useful as predictors of psychosis-proneness. In studies of individuals with schizophrenia and schizophrenia-spectrum disorders, SAS scores are elevated and appear to have state independence with generally stable elevations of scores over time and through variable levels of active positive symptoms of psychosis (Blanchard et al., 2001; Blanchard et al., 1998; Burbridge and Barch, 2007; Horan et al., 2008; Schurhoff et al., 2003). SAS scores are also elevated in individuals with schizoid, schizotypal and paranoid personality disorders as determined by the DSM-IV TR Axis II criteria (Berenbaum and Oltmanns, 1992; Blanchard et al., 1994; Blanchard et al., 1998; Camisa et al., 2005; Chapman et al., 1976). In samples of college students, those with relatively high SAS scores exhibit symptoms of schizotypal and schizoid personality disorder, self-report psychotic-like experiences and are more

likely to be diagnosed with schizotypal, paranoid, or schizoid personality disorders or eventual schizophrenia spectrum disorders (Camisa et al., 2005; Gooding et al., 1999; Gooding et al., 2005b; Horan et al., 2007; Kwapil, 1998; Kwapil et al., 2002; Mishlove and Chapman, 1985). In addition, preliminary evidence has suggested that a combination of SAS and MIS may add additional predictive power (Horan et al., 2007; Kwapil et al., 2013).

As with the MIS, direct associations have been reported between elevated SAS scores and cognitive limitations reported in people with schizophrenia spectrum disorders (Collins et al., 2005; Gooding and Braun, 2004; Gooding et al., 2006; Gooding et al., 2005a; Gooding and Tallent, 2003; Gooding et al., 2001). Higher SAS scores are associated specifically with deficits in sustained attention (Kwapil and Diaz, 2000), working memory and executive functioning (Gooding et al., 1999; Tallent and Gooding, 1999), as well as with psychophysiological abnormalities seen in schizophrenia spectrum patients such as smooth pursuit eye tracking and increased errors on an antisaccadic task (Gooding et al., 2000; Gooding et al., 2005a).

1.4 Objectives

The aim of this study is to find associations between suspected risk factors for psychosis and higher scores on psychosis proneness scales of both positive and negative schizotypy in a population of local high school students.

1.4.1 Hypothesis I – Childhood trauma will be associated with psychosis proneness

Childhood trauma will be associated with elevated psychosis proneness scores on both the MIS and/or SAS. There is clear evidence in the literature that childhood trauma is associated with later onset of psychosis (Varese et al., 2012). In addition, childhood trauma is linked to psychotic-like experiences or subthreshold symptoms in the general population; therefore the population of young people should be ideal to capture this effect (Addington et al., 2013). The MIS and SAS are presumed to be sensitive to psychosis proneness and schizotypy and are well suited to the participant population (Chapman et al., 1994).

1.4.2 Hypothesis II – Prenatal influences and obstetric complications will be associated with psychosis proneness

Obstetric complications have long been associated with schizophrenia in the literature (Cannon et al., 2002). An excess of OCs during pregnancy or birth is anticipated to be linked to elevated MIS and SAS scores of the offspring. Furthermore, prenatal maternal life events or PNMS will be associated with higher MIS and SAS scores. Several studies have suggested that prenatal maternal stress may be translated *in utero* to the child, resulting in possible biological vulnerabilities to later stress and mental health problems (Charil et al., 2010; Reynolds et al., 2013).

1.4.3 Hypothesis III – Cannabis use will be associated with psychosis proneness

There is overwhelming evidence that cannabis is associated with psychosis (van Winkel and Kuepper, 2014). In addition, cannabis used before the age of 16 is

associated with a greater likelihood of later psychosis (Arseneault et al., 2002). An association between cannabis use at least once and elevated psychosis proneness scores on the MIS and SAS is anticipated. With our young local sample, I did not expect any chronic substance abuse problems; however, those who reported use in the past 30 days may be considered to use more often, and this could yield a greater association with the schizotypy scales.

1.4.4 Hypothesis IV – Vulnerabilities considered together will result in a synergistic effect of elevated psychosis proneness

The etiology of psychosis is complex and onset is most likely related to a confluence of several genetic and environmental factors. If we consider our vulnerabilities together, we may find additive or synergistic effects on psychosis proneness scales. Several studies have already considered vulnerabilities together, such as the possibility that cannabis use and childhood trauma work synergistically to produce a later psychosis (Henquet et al., 2008), and a recent paper suggested that the transition to psychosis is mediated by many environmental influences on those with an underlying genetic vulnerability (van Nierop et al., 2013). In addition, in studies considering only adverse life events, as number of adversities increases, so does the odds of psychosis onset (Heins et al., 2011). Therefore, different types of insults, such as prenatal stressors and OCs, might be anticipated to act in an additive or multiplicative manner on psychosis proneness.

2.0 Methods

2.1 Participants

Participants from Edmonton and the surrounding area were obtained as a subset sample of a relevant study undertaken from September 2008 through January 2011. Participants were predominantly in academic grade 11 and registered in Career and Life Management (CALM) or Psychology classes. The school board, principal and teacher agreed to allow the study educator into these classes during regular class time to provide an online survey of high school students' knowledge and attitudes about psychosis before and after an educational presentation. Consent forms were distributed prior to the educational session and required parental signature. A total of 437 consent forms were returned. Of the 437 eligible students, 310 attempted at least one survey, 292 completed the psychosis proneness scales and 221 responded to the life adversity scales and we used this population for all our analyses (n = 221, n_{males} = 89, $n_{females}$ = 131, $n_{unspecified}$ = 1). Following completion of the survey, participants were queried as to their interest in further investigations (n = 172) and 73 indicated this interest (mean age = 17.4). As part of the further investigation, we requested contact information from each participant's mother so that she could complete a brief interview by phone or email, with this information to be paired with the student's information (n = 73). Of the 221 students included in the full sample, 66% identified as Caucasian (n = 146), 11% Metis or First Nations (n = 24), 10% Asian (n = 22), and 13% other (n = 29).

2.2 Measurement

2.2.1 Survey layout

This study was approved by the Health Research Ethics Board (HREB) at the University of Alberta. Socio-demographic data were collected from the students regarding sex, ethnicity, and family economic status. The web-based survey was designed in consultation with the Addiction and Mental Health Research Laboratory (AMHRL) of the University of Alberta. The AMHRL have previously implemented several large scale studies, including four province-wide school-based surveys of youth alcohol, tobacco and other drug use including collection of data for Health Canada's Youth Smoking Survery and AADAC's Alberta Youth Experience Survey (Alberta Health Services, 2009).

From the mothers, we obtained information regarding the participant's birth weight, as well as whether she or the biological father of the child had sought professional help for issues regarding emotional or mental health or substance use.

2.2.2 Psychological risk (dependent variables)

2.2.2.1 Social Anhedonia Scale

The SAS (also known as the Revised SAS, or R-SAS in the literature following an update by the group in 1982) assesses symptoms that may indicate proneness to the negative syndrome of psychosis (Chapman et al., 1976; Eckblad et al., 1982). The SAS is a 40-item, true/false questionnaire where a pathological response is indicated following a "true" response in half of the items (e.g. "I attach very little importance to

having close friends") and a "false" response for the remaining half (e.g. "I have always enjoyed looking at photographs of friends"). The final score consists of the sum of pathological responses.

2.2.2.2 Magical Ideation Scale

The MIS assesses symptoms that may indicate proneness to schizotypy and the positive syndrome of psychosis (Eckblad and Chapman, 1983). The MIS is a thirty item, true/false questionnaire regarding various magical beliefs and delusional experiences such as thought transmission, thought withdrawal, beliefs in conspiracy theories, and superstitions, among other aberrant beliefs. The final score consists of the sum of pathological responses.

2.2.3 Vulnerabilities (independent variables)

2.2.3.1 Stressful life events

Questions regarding stressful life events were selected from the Childhood Traumatic Events Scale (Pennebaker and Susman, 1988). The original scale included six traumatic experiences: death of someone close, divorce or separation of parents, experience of violence, experience of sexual abuse, having a serious illness or injury, and any other major upheaval that they thought may have shaped their life or personality in a significant way. For this survey, we used only four questions, omitting queries regarding violence and sexual abuse owing to the sensitive nature of these questions and our target population being minors. The retained questions align with other key questions on measures of childhood adverse events including the Childhood

Trauma Questionnaire (CTQ; Bernstein & Fink, 1998) and the Adverse Childhood Experience questionnaire (ACE; Felitti et al., 1998).

2.2.3.2 Maternal stress (medical and psychological)

In a follow-up sample, interested participants' mothers responded to eight queries regarding medical complications during and after pregnancy. Information collected pertained to gestational diabetes, bleeding during pregnancy, pre-eclampsia, pre-term labour, emergency C-section, congenital malformations of the baby, postpartum bleeding that needed medical attention, birth weight of the child, or any other complications they were asked to describe. The mothers were also asked whether they, and/or the child's biological father had ever been in contact with a doctor, psychologist or counselor about their emotions, mental health or substance use in their lifetime.

The mothers were also asked if they had experienced 13 specific life events during pregnancy in an effort to measure possible PNMS. These included; relocation, arguments with their partner, hospitalization of a family member, financial difficulties, bereavement, alcohol or drug problems of a close family member or friend, partner not wanting the pregnancy, separation or divorce, loss of employment (both for the mother or for their partner), physical fights, incarceration of their partner, and/or homelessness.

2.2.3.5 Substance Use

All participants were given the Alberta Alcohol and Drug Abuse Commission Recent Drug Survey (AADAC-RDS) to determine recent drug use patterns (Wild et al., 2006). The 10-item scale quantifies frequency of use in the previous 30 days of alcohol, cannabis, methamphetamine, crystal methamphetamine, cocaine, crack, stimulants,

and MDMA/ecstasy. The survey includes additional questions regarding frequency of alcohol abuse.

2.2.4 Analyses

Initially we ran simple correlations (parametric, Pearson's for normally distributed data; non-parametric, Spearman's, for non-normally distributed data). For further analyses, we used ANOVA and linear regression models. Specifically, the MIS and SAS scales produced non-normal distributions; however we were able to use parametric analyses (i.e. linear regression models) since the residuals were normally distributed. Where associations were found, 2-tailed p values were reported. The threshold for nominal significance was set at 0.05 (uncorrected for multiple testing).

In addition, standardized z-scores were calculated for the MIS and SAS to adjust for gender differences using normative data from separate male and female samples (Chmielewski et al., 1995). The z-scores were used for all analyses of the MIS and SAS. For preliminary analyses, a combined psychosis proneness score was calculated by averaging the z-scores for the MIS and SAS.

3.0 Results

3.1 Hypothesis I

Adverse events (AEs) were common in our sample. Ninety-one percent of the sample reported at least one adverse event in their life and 69% endorsed multiple adverse events. Death of a close friend or family member was endorsed by 68%, having been extremely ill or injured was endorsed by 44%, major upheaval such as divorce or

separation was endorsed by 37%, and other major event that may have shaped their lives or personalities was endorsed by 63%. Figure 2 shows that the endorsement by number of adverse life events was approximately normally distributed.

Figure 2. Percentage endorsement by number of adverse life events.

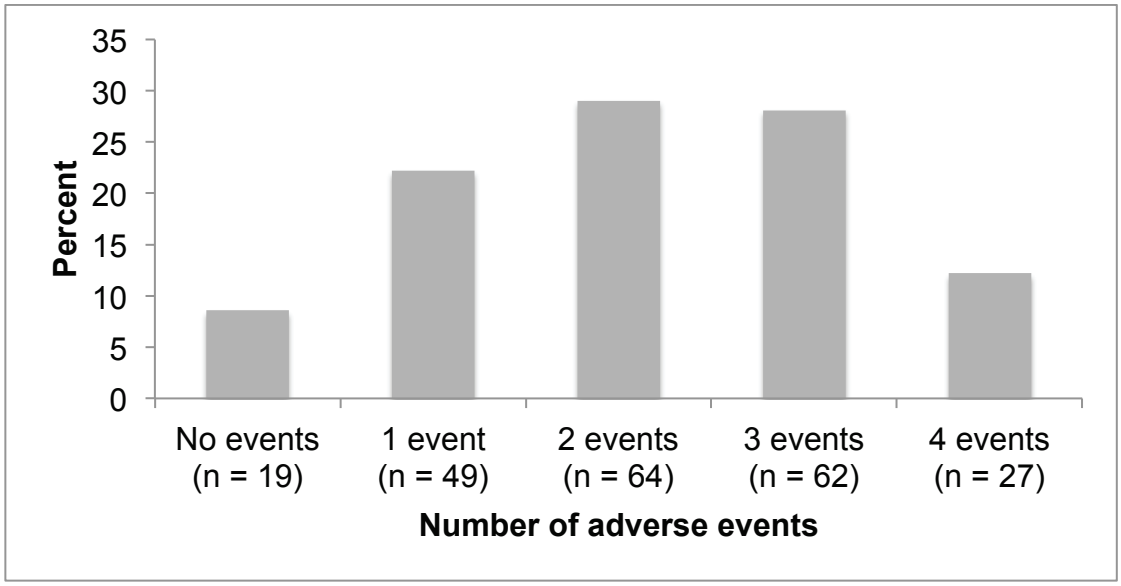
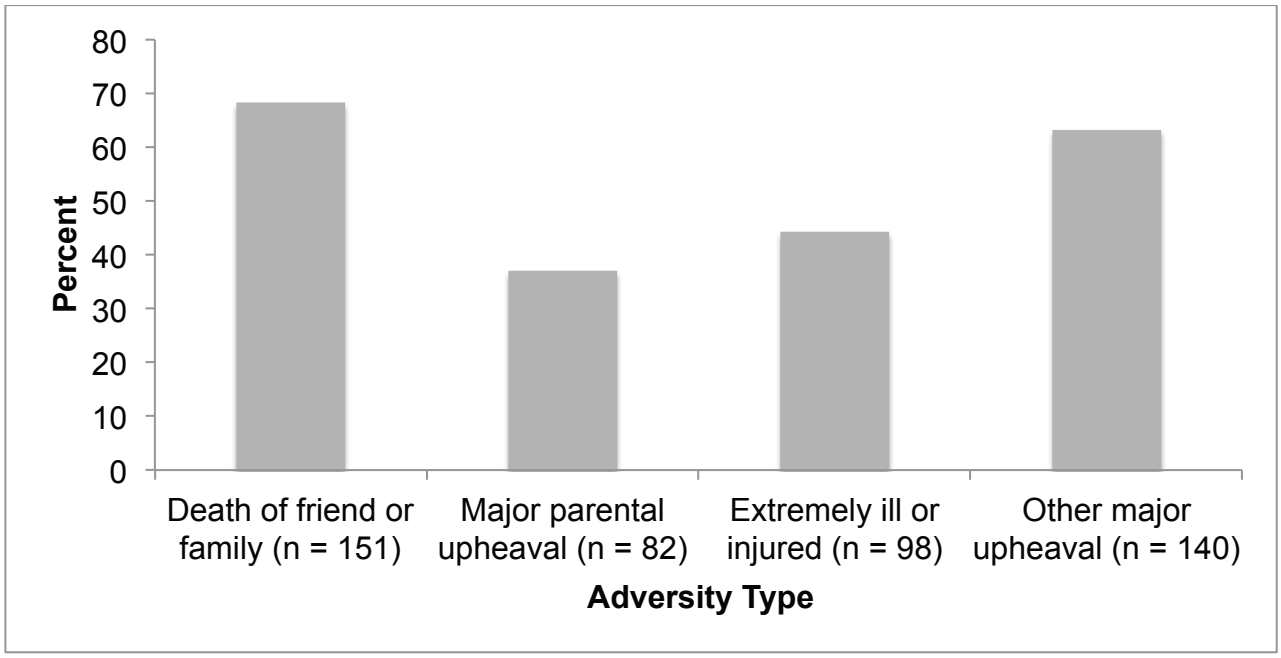


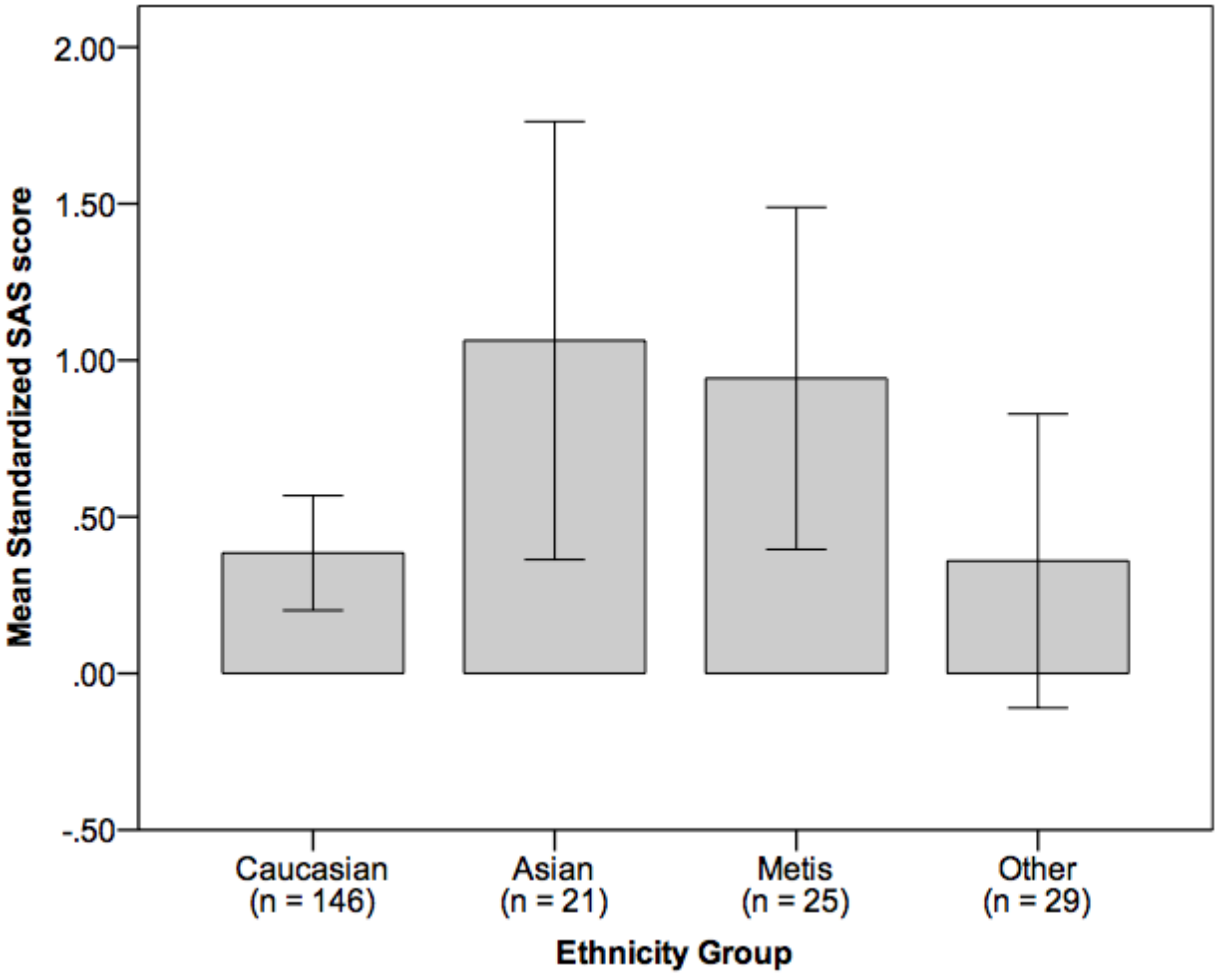
Figure 3. Endorsement of adverse events by type.



Analyses were undertaken to see if AEs were correlated with psychosis proneness (MIS and SAS) (Table 1). AEs were correlated with MIS ($\rho = 0.31$, $p < 0.001$); however, there was no correlation of AEs with SAS ($\rho = 0.06$, $p = 0.362$).

Further analyses included linear regression to determine the strength of the associations including covariates (Table 1). Covariates that were considered included gender and ethnicity, and neither had any statistically significant effect for the MIS on ANOVA analyses. However, ANOVA analyses showed ethnicity was significant for the SAS ($F = 2.51$, $p = 0.031$) and mean standardized SAS score appears to be disproportionately higher in the Asian and Metis ethnicity groups (Figure 4). MIS was predicted by AE score (standardized $\beta = 0.32$, $p < 0.001$). SAS was not associated with AEs (standardized $\beta = 0.09$, $p = 0.165$).

Figure 4. Mean standardized SAS score by ethnicity group (mean with 95% CI shown).



On an exploratory basis, a combined proneness score was created by averaging z-scores of the MIS and SAS (Table 1). Overall proneness score was associated with AEs (standardized β = 0.23, p = 0.001), but not as strongly as MIS and AEs alone and can likely be attributed to the strong association between MIS and AEs, and not to the contribution of SAS to the equation.

Table 1. Pairwise correlations and linear regression results for risk factors (independent variables) and psychosis proneness scales (dependent variables).

	MIS					SAS					Combined Proneness Score				
	ρ	*p*	*Std. β*	*t*	*p*	*ρ*	*p*	*Std. β*	*t*	*p*	*ρ*	*p*	*Std. β*	*t*	*p*
SAS	0.38	***<0.001***	.		.	.	.	.		.	.	.	.		.
Adverse Events	0.31	***<0.001***	0.32	4.92	***<0.001***	0.06	0.362	0.09	1.39	0.165	0.20	***0.004***	0.23	3.46	***0.001***
OC	0.15	0.220	0.02	0.18	0.858	0.03	0.835	0.05	0.37	0.714	0.09	0.456	0.05	0.39	0.699
PNMS	0.04	0.755	0.06	0.52	0.604	-0.08	0.513	-0.11	-0.94	0.351	-0.07	0.564	-0.04	-0.32	0.748
Cannabis Use	0.18	***0.008***	0.18	2.75	***0.006***	-0.02	0.744	-0.01	-0.08	0.936	0.10	0.163	0.09	1.34	0.181

Linear regression equations regarding SAS included ethnicity as a covariate

3.2 Hypothesis II

Over half (54%) of the mothers endorsed at least one pre- or peri-natal medical complication (Figure 5). The graph below describes percent endorsement of each queried OC (Figure 6). The greatest percentage of OCs was other medical concerns not specified in the questionnaire, although the mothers did elaborate: other events included jaundice of the baby, the requirement of a cervical stitch, and in one case broken ribs. Life events in pregnancy were also very common, with 59% endorsing at least one or more (Figure 5). Endorsement of prenatal life events appears in the graph below (Figure 7).

Figure 5. Percentage of OC and prenatal life event endorsement.

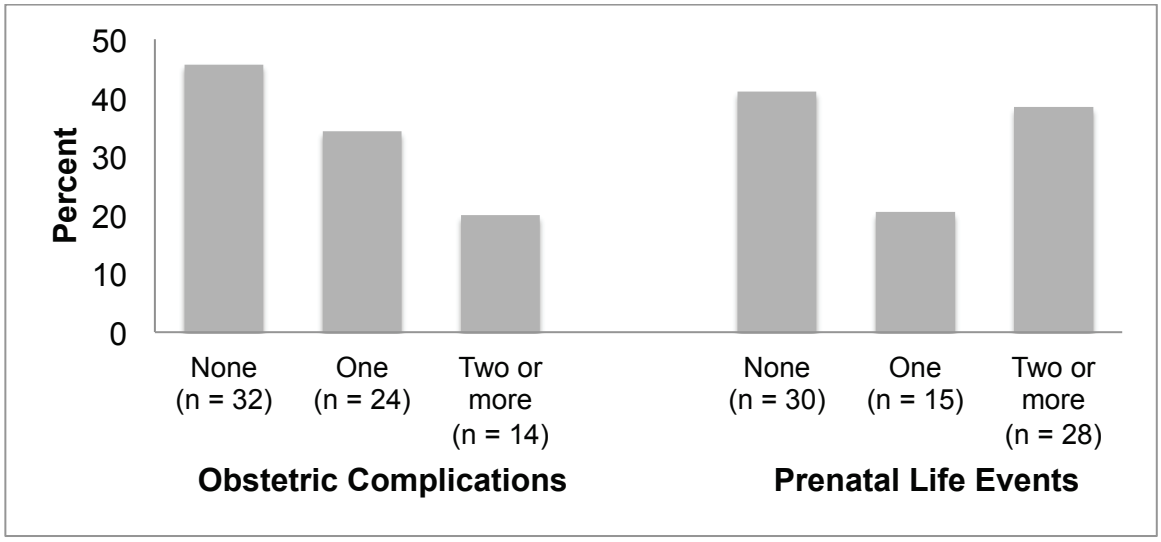


Figure 6. Percentage of obstetric complications endorsed by type.

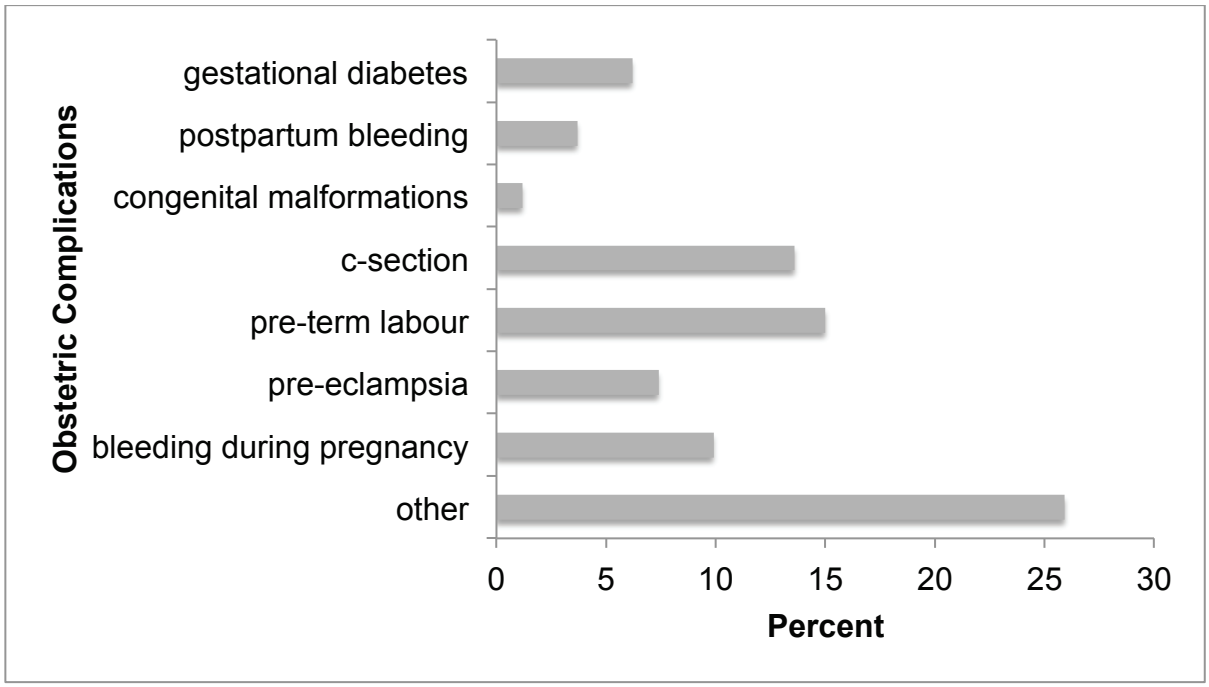
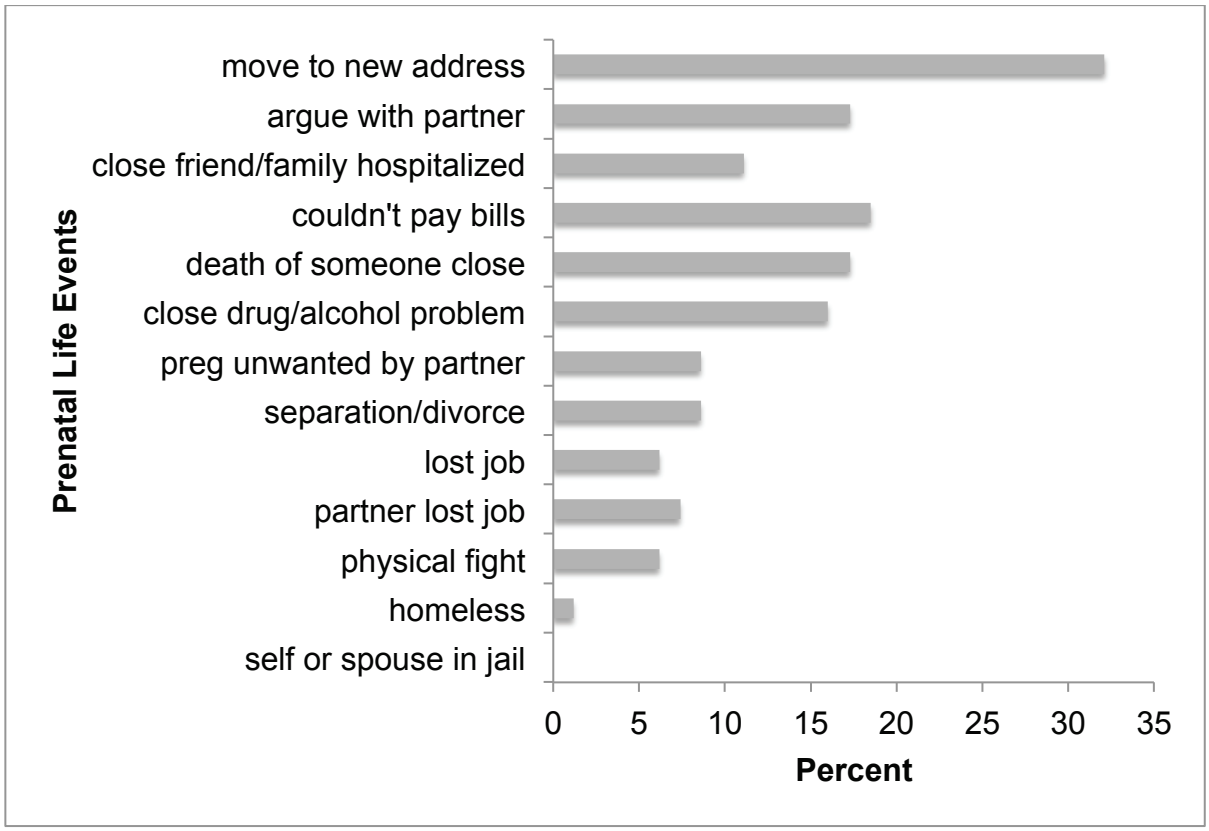


Figure 7. Percentage of prenatal life events endorsed by type.



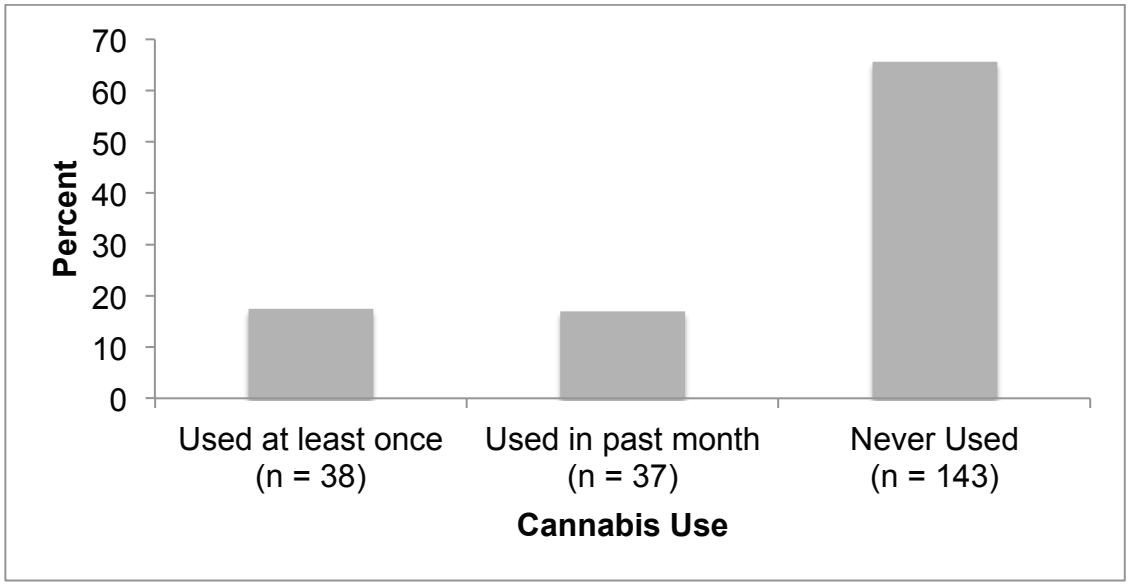
In initial correlational analyses, neither OCs nor PNMS counts were correlated with either psychosis proneness scale. Stratification of the sample by OC or PNMS count (0 events or at least 1 event) resulted in a trend for an association for only OCs with MIS score (Mann-Whitney U test, $p = 0.087$). Sensitivity analyses were then undertaken as follows. Attempts to stratify the data meaningfully continued to yield no effect with the proneness scales. There were no significant correlations between individual OCs or PNMS with MIS or SAS. Furthermore, no correlations or associations were found between OCs or PNMS with overall proneness score. In addition, no correlation was found between birth weight and proneness score, nor was there any correlation

between proneness and if either parent had sought help for mental health or addiction related issues. In a further exploratory analysis, the item regarding the move to a new address was removed from the PNMS sum, as one table ranking the stress associated with different life events (Holmes and Rahe, 1967) estimates that this may be less stressful than the other items in our questionnaire, and was highly reported in the sample. The sum of the remaining items resulted in no correlation on either the MIS (ρ = 0.06, p = 0.607) or SAS (ρ = .-0.06, p = 0.637), without reduction of sample size.

3.3 Hypothesis III

Cannabis use was common in our young sample with 34.4% of participants reporting use at least once in lifetime. In addition, half of those who endorsed cannabis use (17.4%) reported using within the past month (Figure 8).

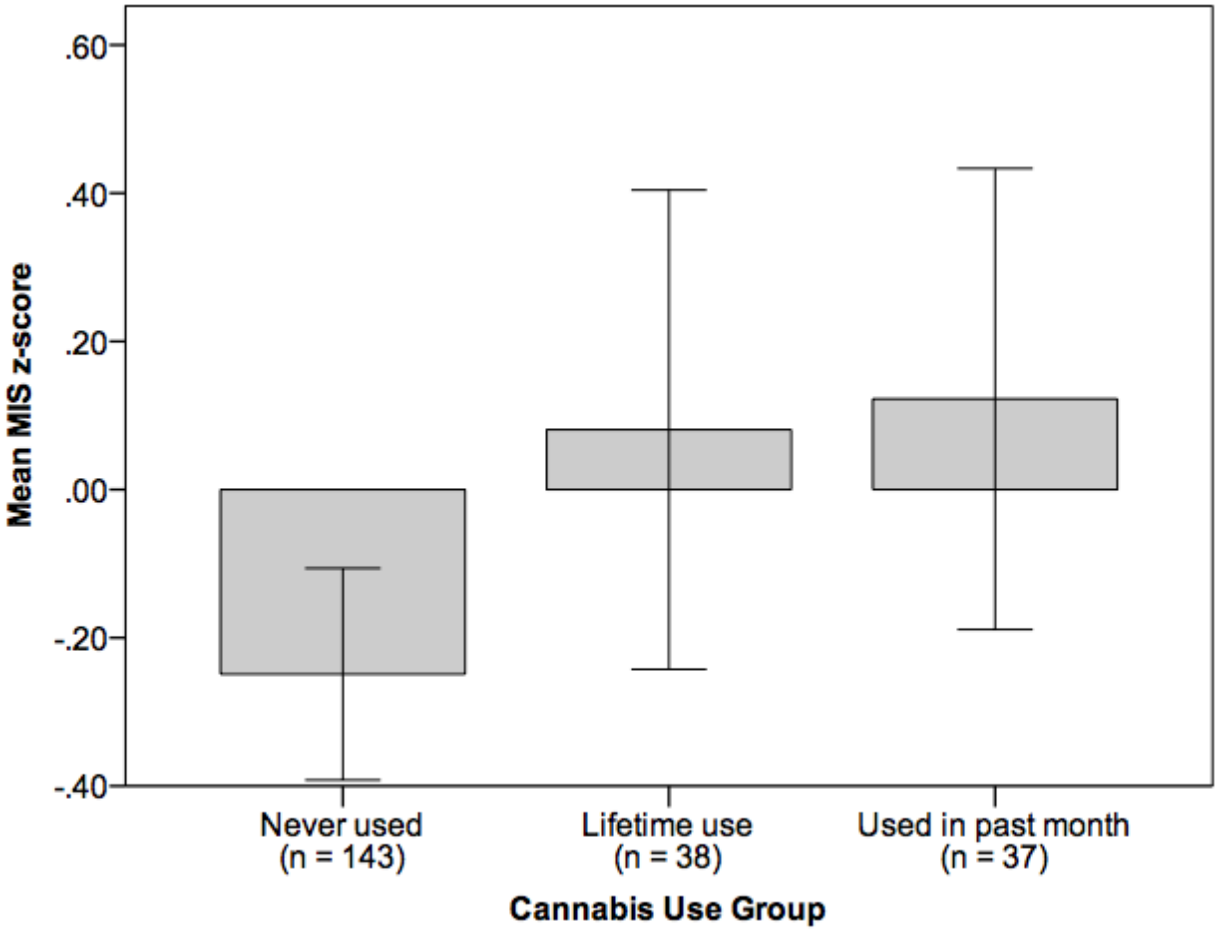
Figure 8. Frequency of cannabis use reported.



The data were stratified into two groups for analysis: lifetime use (used at least once), versus never used. Lifetime cannabis was associated with MIS score (Mann Whitney U test, $p = 0.008$); however there was no association with the SAS. Linear regression also yielded a significant association between cannabis use at least once and MIS score (standardized $\beta = 0.18$, $p = 0.006$). Covariates considered were gender and ethnicity, however neither showed a significant interaction with cannabis use. Lifetime cannabis use was also significantly correlated with the adverse events score ($r = 0.26$, $p < 0.001$) and was significantly associated with AE score in a linear regression (standardized $\beta = 0.26$, $p < 0.001$).

Further analysis considered whether those who used cannabis in the past month may be considered to be greater users and therefore including this in a cannabis use group as follows: never used, lifetime use at least once, and use within the past month (Figure 9). Using this as a predictor gave a significant result on MIS score (standardized $\beta = 0.18$, $p = 0.010$), similar to that gained by the previously used cannabis variable.

Figure 9. Cannabis use category by standardized MIS score (mean with 95% CI shown).



3.4 Hypothesis IV

ANOVA and linear regression analyses were utilized to evaluate all risk factors together to try and better predict psychosis proneness. The adjusted R^2 was used to report how much variance each variable predicted (Table 2). For any risk factors correlated with each other at a significance level <0.10, they were considered non-independent, and therefore not taken forward into a regression model together (Table 4). However,

separate ANOVAs including combinations of variables were nonetheless run, in order to estimate sizes of any effect on the variance of standardized MIS score (Table 2). Thereby, the strong association between AEs and MIS was seen to drive most of the significant associations reported in Table 2. There was nonetheless a small increase in the amount of variance accounted for in the MIS scale when AEs were combined with PNMS sum and OC sum (from 0.10 to 0.12). Similarly, linear regression showed a slight increase in standardized β score when AEs were combined with PNMS sum and OC sum separately, although with less significance (Table 3).

Table 2. Contribution of individual and combinations of risk factors to variance in standardized MIS score by ANOVAs.

Risk Factors by MIS in analysis	Adjusted R^2	F Change	*p*	df_1, df_2
Adverse Events	0.10	24.22	***<0.001***	1, 219
OC	0.01	0.03	0.858	1, 68
PNMS	-0.01	0.27	0.604	1, 71
Lifetime Cannabis	0.03	7.56	***0.006***	1, 216
Adverse Events + Cannabis + OC + PNMS*	0.08	2.55	***0.047***	4, 64
Adverse Events + Cannabis*	0.10	13.18	***<0.001***	2, 215
Adverse Events + PNMS	0.12	5.80	***0.005***	2, 70
Adverse Events + OC	0.12	5.46	***0.006***	2, 67
Cannabis + OC	0.00	0.97	0.384	2, 66

*These terms included correlated variables.

Table 3. Linear regression results of the contribution of individual and combinations of risk factors on standardized MIS score.

		Std. MIS		
		Std. β	*t*	*p*
Adverse Events		0.32	4.92	***<0.001***
Cannabis Use		0.18	2.75	***0.006***
Adverse Events and Prenatal Events	AEs	0.38	3.36	**0.001**
	PNMS	-0.01	-0.08	0.935
Adverse Events and Obstetric Complications	AEs	0.38	3.30	**0.002**
	OCs	0.05	0.48	0.635
Cannabis Use	Cann Use	0.17	1.39	0.171
	OCs	0.01	0.06	0.955

On an exploratory basis, because an additive model combining OCs with AEs had little effect, we combined the variables using a formal interaction term. This gave a non-significant result for the interaction term for both OCs ($p = 0.858$) and PNMS ($p = 0.869$) when combined with AE score, as well as resulted in less significant associations for AEs and OC sum as well as for AEs and PNMS sum when the interaction term was included (AEs: $p = 0.114$, OCs: $p = 0.214$; AEs: $p = 0.050$ PNMS: $p = 0.295$).

3.5 Secondary analyses

MIS and SAS scores were correlated with each other ($\rho = 0.38$, $p < 0.001$), and scores on the MIS predicted SAS scores (standardized $\beta = 0.38$, $t = 5.98$, $p < 0.001$). Self-reported mental and emotional health was correlated with scores on the MIS ($\rho = 0.35$,

$p < 0.001$), on the SAS ($\rho = 0.24$, $p = 0.001$), with AEs ($r = 0.23$, $p = 0.001$), and with lifetime cannabis use ($r = 0.25$, $p < 0.001$) (Table 4).

Given the female majority in our sample in contrast to the male majority in many studies of schizophrenia, further exploratory analysis of males only was undertaken for the larger sample (221) to investigate correlations or associations of the risk factors with either proneness scale in males only (n = 89). There were no obvious differences in ethnicity (Caucasian = 60%, Asian = 11%, Metis = 10%, Other = 19%), reported physical health, mental and emotional health or family SES from the full sample of 221. For males only, standardized MIS and SAS scores remained highly correlated ($\rho = 0.40$, $p \leq 0.001$), and MIS scores were correlated with mental and emotional health ($\rho = 0.30$, $p = 0.009$), while standardized SAS scores were not ($\rho = 0.03$, $p = 0.773$). In addition, while SAS scores remained uncorrelated with AE score ($\rho = 0.126$, $p = 0.238$), MIS scores were highly correlated with AE score ($\rho = 0.49$, $p \leq 0.001$), and AEs strongly predicted MIS score on linear regression ($\beta = 0.45$, $p \leq 0.001$). Furthermore, the amount of variance accounted for increased to around 19% on ANOVA ($R^2 = 0.19$, $p \leq 0.001$). Male only analysis (n = 87) of lifetime cannabis use was not significantly correlated with either proneness scale (MIS $\rho = 0.16$, $p = 0.144$; SAS $\rho = -0.06$, $p = 0.589$) and no significant associations were found on linear regression for either proneness scale with lifetime cannabis use. AE score and cannabis score remained correlated at a trend level and therefore were not further considered together in linear regression.

Table 4. Correlations.

	Std MIS	Std SAS	Gender	Ethnicity	Family SES	Physical health	Mental & emotional health	AEs	OCs	PNMS
	ρ	*ρ*	*r*	*r*	*r*	*r*	*r*	*r*	*r*	*r*
Standardized SAS	**0.38***** n = 221	.								
Gender	-0.08 n = 220	-0.02 n = 220	.							
Ethnicity	0.07 n = 221	0.09 n = 221	**-0.13*** n = 220	.						
Family SES	0.07 n = 194	**0.12**+** n = 194	0.00 n = 193	0.09 n = 194	.					
Physical health	**0.25***** n = 192	0.11 n = 192	0.04 n = 191	0.05 n = 192	**0.27***** n = 192	.				
Mental and emotional health	**0.35***** n = 195	**0.24***** n = 195	**0.15*** n = 194	0.07 n = 195	**0.22**** n = 194	**0.51***** n = 192	.			
AEs	**0.31***** n = 221	0.06 n = 221	0.07 n = 220	0.05 n = 221	0.11 n = 194	0.04 n = 192	**0.23***** n = 195	.		
OCs	0.148 n = 70	0.03 n = 70	0.04 n = 70	0.11 n = 70	**0.21**+** n = 66	0.07 n = 64	0.11 n = 66	-0.09 n = 70	.	
PNMS	0.037 n = 73	-0.08 n = 73	**0.21**+** n = 73	-0.06 n = 73	**0.22**+** n = 69	0.11 n = 67	0.19 n = 69	0.19 n = 73	**0.23**+** n = 70	.
Lifetime cannabis use	**0.18**** n = 218	-0.02 n = 218	0.10 n = 217	0.00 n = 218	0.03 n = 192	0.05 n = 190	**0.25***** n = 193	**0.26***** n = 218	0.08 n = 69	**0.27*** n = 72

+ p ≤ 0.10, * p ≤ 0.05, ** p ≤ 0.01, *** p ≤ 0.001

4.0 Discussion

The objective of this analysis was to assess psychosis proneness in a group of local young people based on their endorsement of experiencing specific risk factors that have been associated with onset of psychosis. We were also looking to see if any of these risk factors worked synergistically to increase an individual's vulnerability to psychosis. Risk factors of interest for this study were childhood adversity, cannabis use, obstetric complications and pre- and peri-natal life events experienced by the mother.

4.1 Adverse events

There was substantial endorsement of life adversity in this sample. Over 90% of the sample endorsed at least one adverse event, while approximately 70% reported multiple life adversities. These numbers indicate a higher prevalence of life adversities in these youth as compared to the previously ascertained prevalence of approximately 40% of the general population including 21 countries across the world (Kessler et al., 2010). In addition, a recent report of ACEs in Alberta indicates that approximately one-third of all respondents endorse at least one type of abuse and almost half endorse at least one type of household dysfunction, and indicate a total incidence rate of ACEs in Alberta of approximately 55% (McDonald et al., 2015). The discrepancy between the Alberta reported ACE statistics and the high endorsement of life adversity in this sample is notable. It may indicate a problem with data collection, over-endorsement by this sample, or possibly an indication that other measures are not capturing full endorsement in their assessments. For example, the ACE Questionnaire used in the Alberta sample does not include an "other" category as the currently used life events

questionnaire does. Perhaps this study has captured an unspecified adverse event, such as the experience of bullying in our young sample, not generally asked about in other measures of life adversity. Bullying as an adverse event was not considered in Kessler's (2010) global assessment of ACEs, nor the recent Alberta study, but has also shown to be linked to psychosis and poor health later on (Fisher et al., 2013; Wolke et al., 2013). Additionally, perhaps the "other" category is capturing life experiences that are considered life changing at the moment for the adolescent, such as the experience of bullying or the ending of a relationship, that may not be considered as pertinent or life changing to the older participants (mean age = 52.4 years) of the recent ACE study (Hardt and Rutter, 2004).

Endorsement of life adversity was highly associated with scores on the MIS suggesting a strong link between positive schizotypy and adverse life events. Adversity in childhood and later life and its link to later psychosis has been well-documented (Beards et al., 2013; Bebbington et al., 1993; Heins et al., 2011; Lataster et al., 2012; Van Os et al., 2014; van Winkel et al., 2013; Varese et al., 2012). As previously mentioned, while childhood adversity alone is not a sole cause of onset of psychosis, it does appear to have a strong influence on the relative and attributable risk for future onset on the background of genetic vulnerability (van Nierop et al., 2013). The biological mechanism whereby life adversities may affect risk for future psychosis may lie in an altered stress response following early adverse life events or trauma, and in conjunction with later stressors, proximal to onset (Beards et al., 2013; Lataster et al., 2012; Raune et al., 2009; Roper et al., 2015). For example, the Hypothalamic-Pituitary-Adrenal axis (HPA axis) that releases and moderates cortisol in the body in response to stress may

be overactive and faulty in those at risk for psychosis (Borges et al., 2013; Collip et al., 2011; Lataster et al., 2013; Lovallo et al., 2012). In addition, it has been suggested that epigenetic processes may facilitate this faulty mechanism; early life adversity combined with other risk factors such as genetic vulnerability and pre- and peri-natal events affect HPA axis functioning, resulting in altered stress responses later in life and increasing the risk for later psychosis (Beards et al., 2013; Fish et al., 2004; King et al., 2005; King et al., 2010).

As it appears that childhood adversity is strongly associated with future onset of psychosis, it is important to ensure the measures are assessing what we intend. Participants in this study are younger than the original CPPS norms completed with college age students. As PLEs are common, and even more so in younger people, these results may reflect an over-endorsement of magical ideation. However, the discrepancy between the ages is very small (approximately 18.5 years for the normative data and 17 years for our sample) and is therefore unlikely to greatly affect the results. In addition, the overall responses from this sample ($mean_{males}(89) = 8.56$, $SD = 5.24$; $mean_{females}(131) = 9.69$, $SD = 5.93$) do appear to match closely to those of the original CPPS normative data for the MIS ($mean_{males}(682) = 8.60$, standard deviation (SD) = 4.97; $mean_{females}(830) = 8.42$, $SD = 5.54$) (Eckblad and Chapman, 1983).

Finally, it is important to assess the predictive value of this association and its ability to reasonably detect psychosis proneness in this sample. The MIS is a well established psychometric that has been useful in detecting sub-clinical psychotic symptoms, and has been shown to be particularly useful when used in conjunction with other measures of psychosis proneness, such as an interview of subclinical symptoms or other

measures of proneness (Chapman et al., 1994; Kwapil et al., 2013; Kwapil et al., 1997). Due to the strong evidence for the link between later psychosis and adverse life experiences, the robustness of the association found in our sample appears sound.

4.2 Cannabis use

Lifetime cannabis use was endorsed at expected numbers based on recent substance use analyses of young people in the province of Alberta (Alberta Health Services, 2009). Lifetime use was associated with higher scores on the MIS, suggesting a link between cannabis use and psychosis proneness in our sample. This is important as research has shown a well established link between cannabis use earlier in life (i.e. before the age of 15, and before the age of 18) to not only psychosis generally, but also earlier age of onset (Arseneault et al., 2002; Di Forti et al., 2014). Of interest, cannabis use was significantly correlated with life adversity in this sample, pre-empting analyses to meaningfully combine their effects. However, it is important to note that some studies have suggested a link between early trauma, later cannabis use and the onset of psychosis. The causal relationship between the two risk factors would need to be considered; perhaps life adversity leads to a vulnerability of cannabis use, or *vice versa*. This analysis shows that adverse events are associated with cannabis use. In addition, there could be an epigenetic, or even genetic, cause that leads to cannabis use as well as susceptibility to life trauma (Harley et al., 2010; Henquet et al., 2008; van Winkel and Kuepper, 2014; Vinkers et al., 2013).

4.3 Prenatal events and obstetric complications

Mothers endorsed several OCs and prenatal life events in our sample. Over half endorsed one or more complications, and almost 60% endorsed a prenatal life event or PNMS (Figure 4). However, there was no association between the results from the mother's questionnaire and psychosis proneness scales of their offspring. There was also no correlation between birth weight and psychosis proneness, nor was there an association between psychosis proneness and those whose parents may have sought help for mental health or addictions. However, there was a small increase in the amount of variance accounted for in the MIS scale when AEs were combined with PNMS sum and OC sum (from 0.10 to 0.12).

There is overwhelming evidence that OCs in particular are associated with schizophrenia in the offspring (Cannon et al., 2002; Dalman et al., 1999; Lewis and Murray, 1987; Mittal et al., 2008). In addition, prenatal life events experienced by the mother are increasingly being implicated in poor health outcomes and psychosis in the offspring (Beydoun and Saftlas, 2008; King and Laplante, 2005; King et al., 2010). As previously mentioned, these are also factors implicated in producing the altered stress response observed in those at risk for psychosis (King et al., 2010; Reynolds et al., 2013).

It is important to consider whether the questions provided to the mothers were useful and valid. The OC questionnaire comprised complications generally considered associated with psychosis, consistent with good face validity for the included questions (Ballon et al., 2008; Cannon et al., 2002). The prenatal life events questionnaire may

have suggested too many life events of variable levels of subjective stress for the small sample size, resulting in a null effect across the board. PNMS endorsement might have been more useful if the mothers suggested a level of stress associated with endorsed events, or a hierarchy of severity of stressors whereby endorsed stressors could then be weighted accordingly as has been employed in early life stressor studies (Holmes and Rahe, 1967). In addition, as the mothers are recalling events from more than 15 years prior, recall bias should be considered.

4.4 Social Anhedonia Scale

No associations were found with any of the risk factors and the SAS. The SAS is well-established tool for assessing psychosis proneness (Chapman et al., 1994; Horan et al., 2007; Kwapil, 1998; Kwapil et al., 2013). Moreover, it has been able to indicate proneness for both positive and negative schizotypy (Kwapil et al., 2012; Kwapil et al., 2013). Having no association in this sample is puzzling, especially as the MIS and SAS are highly correlated and scores on the MIS predict scores on the SAS, suggesting that the risk factors for psychosis associated with MIS would be likely to affect scores on the SAS to some extent.

One potential explanation for this discrepancy is that the SAS is sensitive to both positive and negative schizotypy (Kwapil et al., 2012; Kwapil et al., 2013). Perhaps our sample, due possibly to its young age, is endorsing only positive schizotypy and little to no negative symptomatology. If so, any effect on the SAS may be better accounted for by the MIS measure. This would also partly explain the strong association between MIS and SAS scores.

Another possibility is that social anhedonia may be more strongly associated with genetic predisposition of psychosis, whereas magical ideation appears to be more sensitive to environmental influences on top of genetic risk (Brambilla et al., 2014; Docherty and Sponheim, 2008; Hay et al., 2001; MacDonald et al., 2001; Tomppo et al., 2012). While relatives of patients with schizophrenia do generally endorse greater rates of schizotypy, the familial effect appears to be stronger for negative symptoms, such as those assessed by the SAS than for positive symptoms (Faraone et al., 2001). In particular, there is an association of the *COMT* Val158Met polymorphism and SAS scores both in patients with schizophrenia and in their biological relatives that is not found with other scales of schizotypy, including the MIS (Docherty and Sponheim, 2008). Therefore, the current assessment of the effects of environmental vulnerabilities, such as life stressors, cannabis use, and prenatal events, may not be affecting baseline scores on the SAS, but may help explain the association of SAS with MIS, as well as the robust association of MIS with these vulnerabilities in this study.

4.5 Limitations of Study

One of the limitations of this study was sample size, in particular for the OCs and prenatal life events questionnaires. There is convincing evidence that pre- and peri-natal events are highly relevant to psychosis and schizophrenia (Ballon et al., 2008; Cannon et al., 2002; King et al., 2010). OCs and psychosis have historically been difficult to study because of small effect sizes and the very high likelihood of the influence of other environmental, epigenetic and genetic factors (Cannon et al., 2002). It

is possible that a larger population with maternal obstetric and life event responses may yield stronger results.

Another limitation of this study is the limited number of life adversity questions. The original questionnaire also asked specifically if the participant had experienced sexual abuse, or physical violence and neglect (Pennebaker and Susman, 1988). While these two items were specifically dropped from the assessment owing to the subject matter and the age of the participants in this study, they are highly relevant questions to assess childhood adversity and traumatic experiences, not only in relation to onset of future psychosis, but also to symptomatology and presentation of future psychotic episodes, in addition to other health implications (Beards and Fisher, 2014; Bentall et al., 2014; Dong et al., 2004; Dube et al., 2003a; Felitti et al., 1998; Kessler et al., 2010; Morgan et al., 2014). In addition, while there is supportive research for accuracy of memories and self-reporting of traumatic experiences in general (Dube et al., 2004), there is also evidence indicating a lack of responding to questions about traumatic experiences unless it is asked about specifically (Drury, 2015).

In addition, the psychosis proneness scales used in this study may have been reinforced by including the CPPS Perceptual Aberration Scale (PerAb) and the Physical Anhedonia Scale (PAS), allowing us to calculate overall positive and negative schizotypy scores as reported by Kwapil and colleagues (Kwapil et al., 2013). An overall schizotypy score may have had a greater effect (accounting for a greater proportion of the variance) with the psychosis risk factors in this study. In addition, an assessment of prodromal symptoms might have been beneficial in addition to the proneness scales.

Finally, another limitation in this study is that it assumes a causal relationship between the psychosis risk factors affecting psychosis proneness and the possibility of later onset of psychosis. It must be considered if the psychosis-prone are more likely to have these life experiences, or if these life experiences contribute to a future psychosis. Some considerations include the biases in sample selection inherent in human studies, as well as confounding of multiple vulnerabilities that are themselves associated or contributory (van Os et al., 2010; van Winkel and Kuepper, 2014). In addition, as there is an accepted genetic component to psychosis, it is possible that there is a genetic contribution to the experience of other vulnerabilities; therefore, the association of each risk factor to psychosis could possibly be loaded by common genetic factor(s) (van Os et al., 2010). While causality is an important issue here, studies should continue to evaluate the gene-environmental effects to better delineate the causes and progression of psychotic illness.

4.6 Future Directions

Further analyses should consider the genetic component in these measures of psychosis proneness. The advances in GWAS analyses for schizophrenia have made studying relevant genes for psychosis and schizophrenia more attainable (Schizophrenia Working Group of the Psychiatric Genomics, 2014), and while environmental and epigenetic influences are highly relevant and likely also necessary to facilitate the onset of psychosis, they do not discount that there must be an underlying genetic predisposition (Cardno et al., 1999; Gottesman and Shields, 1967; Lenzenweger, 2015; Lenzenweger et al., 2005; McGuffin et al., 1984; Meehl, 1962).

Another area of further study should assess resiliency of the individuals and how this might affect the likelihood of onset of psychosis. This study reviewed environmental factors that have shown increased likelihood of future psychosis; however, there must be environmental and personality factors that also decrease this likelihood, even for individuals who may have been exposed to several risk factors (Boyette et al., 2014; Pruessner et al., 2011). Social connectedness and support, self-esteem, personality type and coping style have all been suggested as possible protective factors for those at high risk (HR) for psychosis (Boyette et al., 2014; Lim and Gleeson, 2014; Pruessner et al., 2011). Better understanding of resiliency and these protective factors may inform the model currently used to determine who might be at HR, as well as being helpful in possible prevention techniques.

Finally, it will be important to consider the biological and psychological mechanisms that might mediate how these environmental risk factors could predispose an individual to a future psychosis. Determining the mechanisms will be useful in targeting treatment and prevention efforts. However, this is especially complex as there is evidence for stress sensitivity (e.g. HPA axis dysfunction), inflammation, morphological differences in the brain, neurotransmitter and hormonal disruption, as well as personality factors that have all been associated with psychosis, as well as with other various other risk factors (Davis et al., 2003; Egerton et al., 2014; Lataster et al., 2013; McCrory et al., 2012; Nordholm et al., 2013; Stone et al., 2007; van Haren et al., 2012; van Winkel et al., 2013; Varese et al., 2012). To complicate the picture further, epigenetics plays a role in many of these biological mechanisms and in the etiology of psychosis. Some innovative work in this area has attempted to delineate the psychological and biological pathways

that specific life adversities might follow to produce specific psychotic symptoms (Bentall et al., 2014; van Nierop et al., 2014). While the evidence is mixed, further research in these areas may be beneficial to improving the signal of certain pathways or mechanisms, thereby guiding future research to further illuminate the etiology of psychosis (Bentall, 2014).

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