FACTORS ASSOCIATED WITH THE ONSET OF SCHIZOPHRENIA AND LONG TERM PSYCHOSIS IN ADOLESCENTS WHO CONSUME CANNABIS:
A SYSTEMATIC REVIEW OF THE EVIDENCE

by

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A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE IN NURSING

in

THE FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES
THE UNIVERSITY OF BRITISH COLUMBIA
(Vancouver)

July, 2015
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Abstract

During adolescence the brain undergoes critical neurodevelopment. It is a time when some teens are at increased risk for developing early onset schizophrenia, and when recreational cannabis use is high. Over the past 25 years, a growing body of schizophrenia research has focused on examining linkages between heavy (daily, or >50 times in a lifetime) cannabis use during adolescence and early onset of the disorder during adolescence. Findings suggest an association between neurodevelopment, heavy cannabis use during adolescence and the development of early onset schizophrenia. To date no systematic review (SR) has provided a summary of the main findings or synthesis of the range of factors or has critiqued methodological quality of existing studies.

The purpose of my thesis was to provide a synthesis which critically appraises the reporting and methodological quality of observational studies examining factors reported to be associated with early onset schizophrenia in adolescents (aged 10 to 19 years) with a history of heavy cannabis consumption. Nine electronic health databases (Google Scholar, the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (DARE), PubMed, MEDLINE, EMBASE, CINAHL, and PsycINFO) were systematically searched to locate relevant studies using predetermined eligibility criteria. Intra-rater reliability was used to reduce selection bias. Data from 16 eligible studies were synthesized using the Gerard method and the STROBE tool was used to appraise reporting and methodological quality of studies.

The results of this SR show a strong positive association between heavy and frequent cannabis use during adolescence and early development of schizophrenia/psychotic symptoms. Findings also indicate that age at which cannabis is first used, genetic
predisposition, and childhood trauma also increase this risk. The methodological quality of these 16 studies was generally strong however reporting on the handling of missing data, the inclusion of both male and female subjects, and power analyses would have strengthened the evidence. Findings of this SR have implications for nurses in areas of education, research and practice. There are also implications for policies amongst policy makers, and knowledge translation amongst youth, their families, and the general public.
Preface

This master’s thesis is an original intellectual product of the author, B. Wagner.

There was no requirement to obtain approval from the ethics committee for this thesis due to the nature of the study design (Systematic Review).
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Acknowledgements

First and foremost I would like to express my most sincere gratitude to Dr. Fay Warnock, my thesis supervisor. Thank you Fay for agreeing to supervise me in this endeavor and for working diligently with me for the last several months on this project. I am truly grateful for your ongoing support, your push to meet various deadlines and milestones, and your encouragement throughout this process. Secondly, I wish to thank two other individuals, Dr. Leanne Currie and Dr. Geertje Boschma, thesis committee members. I thank you for agreeing to work with me on this project as you both have enriched this thesis with your extensive knowledge in your respective areas of expertise. Although we were not fortunate enough to meet face-to-face I can say that I always felt you were available and that you were close by. So again, I thank all of you Fay, Geertje and Leanne for your constant encouragement, your support, and your availability over the last several months, your contribution into this project is appreciated immensely!

Equally so, I would like to thank my family. To Cory, Ehra and Autumnne, thank you for your patience and understanding when I was not always available to you. Thank you for allowing me the time and the space to work on my project. I am grateful for your constant encouragement, especially in those times that I doubted my ability to continue on. To my Mom and Dad, and my many other relatives, I appreciative your cheering me on and rallying tirelessly behind me. When times were tough, you were my cheering squad…and believe me, there were many times when I needed those cheers more than you know.

To my friends and to my colleagues at work, your interests in my project as well as your many pats on the back have convinced me that this endeavor is something worth pursuing. We have had many stimulating discussions which have not only increased my
interest in this subject, but have provided me with a greater understanding and a broader perspective on this topic as well.

Lastly, thank you to the British Columbia Nurses Union (BCNU) for financially supporting this academic endeavor through the member’s education bursary on more than one occasion.

This journey into completing my masters of nursing was once something I only dreamt about, it was something I hoped to accomplish “one day”. With the ongoing encouragement and support from my mentors, my family, my friends, my colleagues, and BCNU, this dream has become a reality. For this I am eternally grateful!
Chapter 1: Introduction

In this chapter, I provide the reader with an introduction of the issues and background that formed the basis for me pursuing this systematic review (SR) thesis study. The chapter begins with a description of the background, is followed by a problem statement, then an explanation of the significance of the research, a statement of purpose as well as a description of the researchable question for this systematic review, and finally a description of the theoretical framework that I used to guide me in my research.

1.1 Background: Schizophrenia

Schizophrenia is a chronic mental condition that is estimated to affect up to 1% of the world’s population (Stuart & Laraia, 2005). The disorder, which is considered to be one of the most debilitating and non-discriminatory types of chronic mental health conditions, is characterized by profound disruptions in perception, thinking, and behaviour, and is associated with a marked decline in psychosocial function (Carrion et al., 2011). Schizophrenia is usually first diagnosed during adolescence or early adulthood (National Institute of Mental Health (USA), 2014), with males more frequently exhibiting symptoms at a younger age than females (Canadian Mental Health Association, 2014; Lewine, 1980; Loranger, 1984). For example, according to Hafner et al. (1998), males are approximately 1.3 times more likely than females to present with symptoms of schizophrenia prior to 21 years of age (Hafner et al., 1998).

According to the Diagnostic Statistical Manual of Mental Disorders 5th edition (DSM-V), to be diagnosed with schizophrenia, an individual must exhibit two or more of the following five symptoms over one month’s duration: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms (American
Psychiatric Association, 2013). Of the minimum two DSM-V symptom requirements, one of the symptoms must be delusions or hallucinations, or disorganized speech (American Psychiatric Association, 2013).

Currently there is no known cure for schizophrenia. Treatment is therefore limited to the management of symptoms through drug and psychosocial support therapies (Grohol, 2014). If schizophrenia is left untreated the individual will inevitably follow a clinical trajectory of continued functional decline, pervasive cognitive impairment, and fluctuations in both positive and negative symptoms (Carrion et al., 2011; Lesh, Niendam, Minzenberg, & Carter, 2011; O’Donnell, 2007; Savilla, Kettler, & Galletly, 2008; Stuart & Laraia, 2005). The earlier schizophrenia is diagnosed the more debilitating the outcomes because symptoms tend to be more frequent, severe, and of longer duration as compared to those who are diagnosed at a later age. Hence early onset schizophrenia can also be regarded as a chronic form of mental illness; highlighting the gravity of this debilitating illness for children and their families. As of yet, no single cause has been attributed to early development of schizophrenia. Moreover, although several potential factors are assumed to contribute to the disorder, including adolescent neurodevelopment and/or heavy recreational use of cannabis, their pathways of association remain unclear.

1.2 Problem Statement

Currently a growing number of studies, including those from the fields of adolescent neurodevelopment and epigenetics, are independently examining or testing the foregoing assumptions as well as other potential contributing candidate factors. However, because such studies are often conducted in isolation of each other, it is difficult to gain comprehensive understanding of findings between or across studies. Importantly, to date no systematic
review (SR) study has provided a synthesis of the existing evidence of the range of factors that have been reported to contribute to schizophrenia in general, or that have examined the specific relationship between heavy cannabis use during the critical period of neurodevelopment in adolescence and the onset of schizophrenia. A synthesis of the findings from the various studies may provide the necessary foundations for future regression analyses and hypothesis testing. This will help clarify the complex pathways of association that may underlie early development of schizophrenia and guide development of targeted mental health prevention and treatment interventions specifically for youth who may be at high risk for developing schizophrenia.

In addition, no SR has been conducted that provides a critique of the methodological quality of this existing evidence. This is problematic because erroneous conclusions may be drawn and it becomes difficult to identify gaps in methodology requiring attention to strengthen the quality of future studies. In this SR, I have provided a critical analysis and summary of the methodological strengths and limitations and quality of the available evidence. Findings from various disciplines published in a variety of journal create difficulties for key stakeholders including policy decision makers to draw conclusions of the existing body of evidence. A summary synthesis of findings from this SR may provide an important basis for developing knowledge translation and dissemination protocols useful to informing key stakeholders, including health care professionals whose interests reside with development and enactment of mental health promotion programs and prevention strategies as appropriate.
1.3 Significance of the Research

Emergent findings suggest that the onset of schizophrenia during adolescence (hereafter referred to as ‘early onset schizophrenia’) is positively and strongly associated with frequent and heavy (daily) use of cannabis (either by inhalation or ingestion) during adolescence (Arseneault, Cannon, Witton & Murray, 2004; Casadio, Fernandes, Murray & Di Forti, 2011; Large et al., 2011; Moore et al., 2007; Schimmelmann et al., 2011; Semple, McIntosh & Lawrie, 2005). In one longitudinal population-based study, early and heavy cannabis use during adolescence was found to be associated with more than a twofold increase in the risk for later development of psychotic symptoms in individuals who had no psychotic symptoms at baseline (OR = 2.64, 95% CI: 1.54, 4.52) (van Os, 2002). Other studies have also shown similar findings, further suggesting that both heavy and early use of cannabis heightens an adolescent’s risk for early development of DSM-V cardinal diagnostic symptoms of schizophrenia (Arsenault et al., 2004).

While the preceding findings provide important information, important questions to consider are whether or not cannabis use alone can be considered a necessary and sufficient factor for triggering early onset of schizophrenia (Arsenault et al., 2004), and why only some adolescents who use cannabis heavily will go on to develop schizophrenia while many others do not. Findings from a recent survey on child and youth substance use in the US (United States) conducted by the National Institute on Drug Abuse provides some answers. The findings showed that of the grade 12 students study participants, over one third (36.4%) reported using cannabis within the previous year, and 6.5% reported using cannabis daily (National Institute on Drug Abuse, 2013). Given the moderate usage patterns reported and that schizophrenia during adolescence occurs relatively infrequent, it may be concluded that...
heavy (daily) cannabis use alone is not a sufficient contributor to the disorder (D’Souza, Sewell & Ranganathan, 2009).

The preceding discussion supports the claim that both individual factors and environmental factors play key roles in early onset of schizophrenia (Gilmore, 2010; Maki et al., 2005). One main line of argument is that the critical period of adolescent brain development may mediate the relationship between early and heavy use of cannabis and early emergence of the disorder (van Os et al., 2002; Henquet et al., 2008). I will elaborate further on this theory and the associated findings in subsequent sections of this thesis paper. It is further argued that epigenetics may alter function and structure of the developing brain in genetically determined ways and that epigenetics in combination with other environmental factors may underlie a heightened risk for early onset schizophrenia in some youth (Roth, Lubin, Sodhi, & Kleinman, 2009).

Epigenetics is the study of changes in gene function, where these changes are considered to occur independently of alterations to primary DNA sequencing (Kiefer, 2007). It is hypothesized that an increased risk for the development of any mental illness, including schizophrenia, may occur as a result of timing and a ‘combined’ effect of both individual factors (i.e., genetic predisposition, neurodevelopment) and exposure to environmental factors that adversely impact normative growth and development and/ or that individual perceives as stressful (i.e., perinatal exposure to influenza and teratogens, obstetric complications, season, geography of birth, urbanisation, immigration, famine and other stresses, early exposure to adversity in life and attachment issues, neglect, abuse and trauma, as well as socioeconomic poverty, etc.) (Leask, 2004; Read, Bentall & Fosse, 2009).
While an individual may have a specific genotype (genetic code) for schizophrenia, it is the phenotype, or interaction between genotype, the critical periods of brain development, and exposures to environmental adversity that contribute to this occurrence. To further explain, an individual may possess the specific gene marker for schizophrenia as a result of genetic inheritance but the disorder would only develop if the individual is undergoing critical periods of neurodevelopment and is faced with environmental stressors or conditions that that individual perceives to be highly aversive (Read et al., 2009). For example, variation in personal and environmental conditions as well as individual differences in perceptions and responses to similar environment conditions, may explain why one identical twin does develop schizophrenia whereas the other one does not.

Conducting a SR at this time is timely given concern in the rise in the trend of young individuals who are consuming cannabis recreationally, and under the guise that it is harmless (Kuehn, 2013; Rey, 2002). Recreational cannabis use is a phrase that refers to the use of cannabis without medical justification and with the intention of altering the state of consciousness and creating positive emotions and or feelings. Findings from the aforementioned US surveillance study on patterns of substance use amongst youth for instance found that 60% of grade 12 student participants reported regular cannabis use to be harmless irrespective of whether they had reported that they used cannabis or not (National Institute on Drug Abuse, 2013). Naïve perceptions or misconceptions of cannabis may stem from perceptions of invincibility and risk taking behavior during adolescence (Dahl, 2004). However, because the reported percentages are high, it calls into question whether adolescent perceptions are being unduly influenced by the opinions and persuasive lobbying efforts of consumer groups who are advocating for the legalization of cannabis for recreational and
medicinal use across North America and subsequent legislative changes (Marijuana Policy Project, 2014; Norml, 2014).

One argument expressed by advocacy groups is that cannabis consumption is safe and effective for treating many psychological, physical as well as neurological conditions, such as Parkinson’s disease (Svrakic et al., 2012). Some of the physiological conditions that cannabis has been known to treat include nausea and vomiting associated with cancer chemotherapy, weight loss from diseases such as cancer and HIV, and other neurologic diseases such as multiple sclerosis, pain syndromes and glaucoma (Seamon, Fass, Maniscalco-Feichtl & Abu-Schraie, 2007). Others also argue that cannabis has relaxing qualities and that it can increase ones creativity and expand an individual’s thinking (Stroup, 2015). Some have also claimed that cannabis is less harmful than other recreationally used legal substances such as alcohol and tobacco (Lachenmeier & Rehm, 2015). Because the preceding arguments by lobbyists are often voiced in the absence of emergent findings pertinent to youth; adolescents may interpret that recreational use of cannabis as safe.

As of February 2015, three states in the United States (Alaska, Colorado and Washington) have legalized the recreational use of cannabis and with Oregon soon to follow in July 2015 (Norml, 2015), however in Canada cannabis use remains illegal across all provinces except for medical reasons and only with a doctor’s prescription or with a nurse practitioner prescription if licence permits in the given province or territory (Health Canada, 2013). In Canada, debates continue as to whether recreational use of the substance should be legalized or decriminalized, and these debates extend to national political parties who vary in the views and roles they have assumed on the issue. For example, the Marijuana Party of Canada is leading the national campaign for legalization of cannabis for recreational use, and
it appears that the Liberal Party also shares this position (Liberal Party of Canada, 2014; Smith, 2013). The New Democratic Party (NDP) objects to legalization but are in support of decriminalization and use of marijuana for medicinal purposes (NDP Policy, 2013; Smith, 2013) and the Conservatives favor maintaining the current status quo (The Conservative Party of Canada, 2013).

In 2013, the Prime Minister’s office of Canada [Conservatives] issued a statement declaring that they intend to keep cannabis use illegal, apart from medical use. In that statement they also made clear that they have no interest in seeing cannabis made more easily available to youth due to potential harmful effects (The Conservative Party of Canada, 2013). As some Canadian adolescents may be at particular risk, it is crucial that all key stakeholders (political parties, consumers, health care professionals, youth and families) be informed of the influence of prevailing opinion on teen perception and subsequent use of cannabis. It is also paramount that teens be provided with a comprehensive summary of evidence not only on risk factors but also on the range of factors currently reported to contribute to early onset of schizophrenia in youth who are heavy users of cannabis and to provide a critical assessment of methodical quality of the findings located.

Although findings from various studies seems to support an association between cannabis use and the early onset of schizophrenia symptoms, these findings tend to come from studies which are conducted in isolation of each other. As a result this hampers research in that it limits full comprehension of knowledge about the range of potential contributory factors as well as their relationships. This SR aims to provide an overall understanding of the current state of the science with respect to the host of risk factors
involved in the development of symptoms of schizophrenia in adolescents who consume cannabis heavily, and the relationship between these factors.

1.4 Statement of Purpose

In response to current gaps and concerns, the twofold aims of my thesis SR study were to provide a synthesis and summary of findings from eligible studies that have examined factors associated with early onset of schizophrenia and to provide a critical appraisal of the methodological quality of the eligible studies that were included in the review. In this SR, I was particularly interested in identifying which factors have been reported to be associated with an increased risk for development of early onset of schizophrenia in adolescents (those aged 10 years to 19 years) who have a history of heavy cannabis consumption. A SR is a systematic, rigorous, critical analysis of current primary evidence which identifies, selects, and appraises the methodological quality of relevant research studies, then synthesizes the findings (identifying the factors as discussed above) to answer a specific research question (Polit & Beck, 2012). The systematic processes and procedures that are employed in a SR are aimed to minimize selection bias and resultant findings provide guidance for best practices on a particular subject of interest (The Cochrane Collaboration, 2014).

1.5 Researchable Question of this Systematic Review (PICO format)

As per the conventions of SRs (Aslam & Emmanuel, 2010) I articulated a “searchable” question using the Population-Intervention-Comparison-Outcome (PICO) format. The PICO format is widely acknowledged in evidence-based medicine and nursing and is regarded as essential to methodological quality and soundness of a SR (Aslam & Emmanuel, 2010). It is specifically used to enable a systematic and focused search of the
literature to efficiently locate relevant studies capable of answering the question at hand (Aslam & Emmanuel, 2010). Accordingly, the PICO formulated research question that was used to guide my SR was: What are the risk factors (I) associated with the development of early onset schizophrenia (O) in adolescents who consume cannabis daily (P)?"

P: Adolescents (10-19 years) who consume cannabis and go on to develop schizophrenia

I: Risk factors that have been associated with onset of schizophrenia in adolescents who consume cannabis daily

C: N/A

O: Early onset schizophrenia (schizophrenia as defined by DSM 5 criteria)

In this SR, the main environmental risk factor (independent variable) is early and daily use of cannabis during adolescence, and early onset of schizophrenia is the main outcome (dependent variable). I did not identify a “C” in my PICO because the types of studies that would be relevant to answering the SR question would be examining risk and measures of association and likely not include a comparison study group (adolescents who consume cannabis but who do not go on to develop schizophrenia).

1.6 Guiding Theoretical Framework

In this SR, I chose to use the neurodevelopmental theory as a guiding framework because it specifically pertains to critical periods of adolescent normative brain development. A further reason is that it provided a biophysiological theoretical framework for understanding potential interaction between individual and environmental risk factors that may confer heightened risk for the development of early onset schizophrenia during this critical period of development (Marenco & Weinberger, 2000; Rapoport, 2005). An
additional important reason was that the framework served as a guide for the selection of
published studies on factors (environmental, individual) which helped to explain or account
for the relationship between heavy cannabis use during adolescence and early onset of
schizophrenia.

According to neurodevelopmental theory, throughout various stages of life the human
brain undergoes various “normal” developmental changes, where in adolescence the
hallmark of normative neurodevelopment involves a unique process of synaptic “pruning and
strengthening” (Blakemore & Choudhury, 2006; Spear, 2013). During this phase, brain cells
and neural connections that are used the least are “pruned” and die off and those that are used
the most become “stronger”, making neurological processing more rapid and efficient
(Blakemore & Choudhury, 2006). Although normative changes in adolescent brain
development are observed in limbic structures (i.e., the hippocampus), they are most notable
within the prefrontal cortex, the part of the brain that is responsible for regulation of complex
cognitive, emotional, and behavioural functioning (Malone, Hill, & Rubino, 2010). A
greater understanding of adolescent brain development is continuing to occur as a result of
ongoing improvement to various imaging technologies (Spear, 2013).

The theory postulates that exposure to an environmental risk factor (i.e., aversive
substances, prenatal complications, viruses, stresses and or traumatic life events, etc.) during
the critical periods of fetal, infant, child or adolescent brain development is likely to cause
disruption in brain development, particularly if the environmental factor interferes with the
cascade of normative brain structuring and neurodevelopmental processes (Rice & Barone,
2000). Furthermore, findings of studies that have examined schizophrenia in children and
that have made use of the neurodevelopmental framework suggest that exposures to such
adversity during critical periods of brain development may result in brain lesions that disrupt and alter brain connectivity and circuitries (Hutchins, 2013; Lewis & Sweet, 2009; Malone et al., 2010) which ultimately produce the symptoms of schizophrenia (Rapoport, 2005; Hutchins, 2013).

Interestingly, cumulative evidence from the preceding sets of studies further suggest that these lesions and subsequent brain changes occur prior to an individual exhibiting overt or detectable signs or symptoms of schizophrenia (Rapoport, 2005; Ehninger, Li, Fox, Stryker & Silva, 2008; Kinros, Reichenberg & Frangou, 2010). Essentially what this means is that a brain lesion may lay dormant until the (normal) developmental processes reach or affect the structures impacted by that lesion (Marenco & Weinberger, 2000). Hence, if exposure(s) to a significant environmental risk factor occurs “after” the critical period of adolescent neurodevelopment (i.e., well into the 20’s) (Johnson, Blum & Giedd, 2009) it is thought that the brain is less vulnerable to lesion formation than if the exposure occurs “during” critical epochs of brain development (Rice & Barone, 2000). As mentioned, neurodevelopment during adolescence tends to be most prominent in the area of the prefrontal cortex, so this may also explain why symptoms of schizophrenia are most evident in the areas of cognitive, emotional, and behavioral functioning.

The preceding findings provide compelling neurobiological rationale for how early onset schizophrenia may be triggered as a result of early exposure to adverse environmental conditions, particularly if exposure occurs prior to, or during, the critical period of adolescent brain development. In addition to underlying genetic factors, the neurodevelopmental framework adds to an understanding of why adolescents may be particularly vulnerable, and the individual differences in this vulnerability. Yet, it is important to identify from the
existing evidence additional factors that may contribute, mediate, or confound the relationship between early heavy cannabis use and early onset of schizophrenia.

In summary, schizophrenia is a devastating, debilitating mental illness that impacts the individual. It is a chronic illness that also impacts families, friends, and society as a whole especially if its onset occurs during adolescence. Despite the research to date, there remains no definitive cause for schizophrenia. Although there appears to be several factors that are thought to contribute to early onset of the disorder including heavy use of cannabis during adolescence, investigation on these factors are conducted in isolation of each other. As a result, it remains uncertain as to which factors are most likely to be contributory or if these factors have interactive or additive effects.

In the next chapter I will present an overview from the literature of the variables and factors, including cannabis use that are believed to heighten the risk for developing schizophrenia during adolescence.
Chapter 2: Literature Overview of Variables and Factors

Guided by the neurodevelopmental framework, this chapter provides an overview of individual and environmental risk factors that are thought to be relevant to the relationship between cannabis use during adolescence and early onset of schizophrenia. I begin by discussing the period of adolescence, followed with a discussion of schizophrenia and cannabis to profile the potential contribution of each variable and how the variables when taken together may relate. I continue by discussing neurodevelopment and genetics as both of these variables present strong arguments for why only some adolescents may go on to develop the disorder whilst others do not. In this section I also discuss the endocannabinoid system because this system has been investigated as a possible link to the onset of schizophrenia, particularly in those who consume cannabis during adolescence. From this literature overview I was able to identify several factors that helped serve as key terms for locating relevant studies for my SR.

2.1 Adolescent Development and Neurodevelopment

Adolescence is a transitional period of human development which ends after childhood and moves through into adulthood. According to the World Health Organization (WHO, 2014), adolescents (teens) are those individuals between the ages of 10-19 years of age. During this period of development, individuals undergo several unique biological and psychological changes (Dahl, 2004) and experience marked changes in both their physical and neurological development at a rate which is unparalleled since infancy (WHO, 2014).

Brain development is arguably the greatest developmental change amongst this population (Luna & Sweeney, 2001). As the brain matures, both structurally and functionally, its development undertakes sophisticated refinement in both the cognitive and
emotional domains (Luna & Sweeney, 2001). The hallmark of neurodevelopment is a unique process of synaptic pruning and strengthening where, during the pruning, brain cells and neural connections that are used the least die off, and those that are used most become stronger (Blakemore & Choudhury, 2006; Spear, 2013). Magnetic resonance imaging (MRI) and other imaging technologies have been shown to be valuable for viewing the neurobiological changes that occur during adolescence and over a lifetime (i.e. the size and connectivity across brain regions) (Spear, 2013). The rapid stage of neurodevelopment that occurs during adolescence is considered a ‘critical’ period because it is during these years that youth are particularly vulnerable to disruptions/interruptions in the normal neurodevelopmental processes and are at increased risk for the development of major mental health disorders such as schizophrenia (Luna & Sweeney, 2001; Casadio et al., 2011; Ho, Wassink, Ziebell, & Andreasen, 2011).

2.2 Schizophrenia

Schizophrenia is a complex syndrome which is characterized by a variety of symptoms which affect perception, thought and behaviour (Canadian Mental Health Association, 2014; National Institute of Mental Health, 2014). A defining characteristic of schizophrenia is a phenomenon described as ‘psychosis’. Psychosis is known to affect a person's perception and thinking where at times that person completely loses touch with reality. The individual with schizophrenia may hear or see things perceived through the senses that others do not, or they may have delusions (i.e., ideas about themselves or others that have no basis in reality). They may also exhibit disorganized speech, rigid (catatonic) behavior, or restricted emotions or flat affect (Canadian Mental Health Association, 2014; National Institute of Mental Health, 2014). Delusions, or hallucinations or thought disorder
lasting for one month or longer represent main DSM-V criteria for diagnosis of schizophrenia (American Psychiatric Association, 2013).

The points of time when symptoms of schizophrenia first appear are important. For example, the earlier the onset of symptoms the more devastating the prognosis will be, particularly if the disorder is left untreated (Ongur, Lin & Cohen, 2009; Sugranyes et al., 2009). Those who are diagnosed with early onset schizophrenia, such as teens, tend to have more frequent and severe symptoms compared to those who are diagnosed at a later age, and as a result, these teens also tend to lose important opportunities for meeting normative social and developmental milestones (Hollis, 2000; Clemmensen, Lammers Vernal & Steinhausen, 2012).

Schizophrenia is considered a significant risk factor for suicide. Suicide has consistently been shown to be the most common cause of premature death amongst those with schizophrenia (Raymont, 2001). The lifetime risk of suicide for those with schizophrenia is estimated to be 10%, (Brugnoli et al., 2012; Jarbin, 2003), and of that 10%, youth and early adult populations are at particularly high risk (Jarbin, 2003). Youth with schizophrenia are approximately three times more likely to commit suicide compared to adults with schizophrenia, particularly during the first two years of the disease (Pompili et al., 2007). Furthermore, youth with early onset schizophrenia and who abuse drugs are at an even greater risk for committing suicide. It is estimated that 70% of these young people (children and adolescents) are at risk for suicide either because they abused drugs and or alcohol, were noncompliant with their antipsychotic medications, or because of a co-occurring paranoia and/or depression (Pompili et al., 2007). Therefore, it is essential that the
health care system employ both early detection and intervention programs, with suicide prevention as a key component (Pompili et al., 2007).

Specific risk factors that have been thought to be linked to early onset schizophrenia include: a familial history or genetic predisposition (Maki et al., 2005; Tsuang, Stone & Faraone, 2001; Vereczkei & Mirnics, 2011); neuroanatomical abnormalities (that can be viewed with magnetic resonance imaging) (Maki et al., 2005); fetal exposure to viruses, toxins or malnutrition (particularly in the first and second trimesters) (Maki et al., 2005); life circumstances perceived to be stressful (Norman & Malla, 1993); older paternal age (Vreeker, Schubart, van Gastel, Kahn & Boks, 2013; Zammit et al., 2003); and the consumption of psychoactive drugs such as cannabis (particularly at high doses and for prolonged periods) during adolescence and young adulthood (Casadio et al., 2011; Maki et al., 2005; Malone et al., 2010; Moore et al., 2007; Mayo Clinic, 2014; Parolaro, 2010). It is suggested that the more risk factors a person has, both individual and environmental, the greater the likelihood of developing early onset schizophrenia. For example, individuals who have a genetic predisposition for developing schizophrenia, and who are exposed to various environmental risk factors will be those who are at the greatest risk (Picker, 2005). The exact mechanism of action between these risk factors, however, has not formally been examined, especially amongst at-risk cohorts of adolescents. What is known is that damage from daily consumption of cannabis use is reported to cause lesions to the prefrontal cortex (Bossong & Niesink, 2010), and for those who end up developing schizophrenia, that this will lead to severe impairment in psychosocial functioning later on in life.

The burden of schizophrenia is considered to impact not only the individual with the condition, but also families, friends and society as a whole (Awad & Voruganti, 2008). For
example, a sizable proportion of people with schizophrenia must rely on others because they may lack insight into symptoms and are unable to maintain employment or care for themselves (Awad & Voruganti, 2008). Responses to having a family member, whether it is a child or a sibling with schizophrenia may include: the evocation of feelings of failure, the burden of caring for someone who is ill, fear or embarrassment of the individual or about illness signs and symptoms, uncertainty about course of the disease, a lack of social support, and an overall stigma that is associated with having a family member with this disease (Brady & McCain, 2005).

2.3 Cannabis

Within the last decade there has been growing evidence that suggests there is a relationship between daily or heavy cannabis consumption, particularly during adolescence, and the onset of schizophrenia (Arseneault et al., 2004; Casadio et al., 2011; Caspi et al., 2005; Dervaux, Krebs & Laqueille, 2011; Large, Sharma, Compton, Slade & Nielssen, O., 2011; Moore et al., 2007; Schimmelmann et al., 2011; Semple et al., 2005; Sevy et al., 2010). The term cannabis refers to various types of preparation derived from the plant Cannabis sativa which contains various chemical compounds known as cannabinoids (Casadio et al., 2011). Cannabis, which is also commonly referred to as Marijuana, contains over 400 various compounds, but delta-9-tetrahydrocanabinol (Δ-9-THC), or THC, is the principle psychoactive cannabinoid compound that produces feelings of euphoria, wellbeing, relaxation, increased creativity, and abstract or philosophical thinking, which is known as being “high” (Hall & Degenhardt, 2009). Other cannabinoids that have also been identified include: cannabidiol (CBD), cannabinol (CBN), tetrahydrocannabivarin (THCV) and cannabigerol (CBG). Symptoms arising from cannabis consumption can vary from person to
person and are dependent on the method of use. For example, cannabis can be inhaled by rolling it into a cigarette, also commonly known as a “joint”, or by using an inhalation device such as a bong, pipe, or a vaporizer (Here to help, 2014). It can also be ingested, either on its own, or by adding it to food or drinking it in the form of a tea (Hazekamp, Bastola, Rashidi, Bender, & Verpoorte, 2007; Here to help, 2014). The effects of inhaled methods tend to manifest more quickly and last for a shorter duration, as opposed to ingested methods which take longer to achieve and can last for much longer (Grotenhermen, 2001). Although it is becoming common to use cannabis for various medical purposes, the majority of individuals, particularly adolescents, are using cannabis recreationally to get “high”. However, the effects for some individuals are not always positive, as paranoia and intense anxiety have also been reported with its use (Hall & Degenhardt, 2009; Hall & Solowij, 1998; Here to help, 2014).

Cannabis is one of the most widely used substances amongst teens and young adults (Bersani, Orlandi, Kotzalidis & Pancheri, 2002; Miller, Johnstone, Lawrie, & Owens, 2006). In Canada alone, approximately 3 out of 10 teens aged 15-17 years of age report having used cannabis in 2002, and of those individuals 10% used cannabis daily (Tjepkema, 2004). The prevalence of cannabis use is suggested to be even higher amongst those with psychiatric conditions including schizophrenia (Barnes, Mutsatsa, Watt, & Joyce, 2006; Machielsen, van der Sluis, & de Haan, 2010). For example, an estimated 25% of patients with schizophrenia also have comorbid cannabis use (Lynch, Rabin & George, 2012).

Daily use, otherwise known as chronic or heavy use, is common amongst teens and pattern of usage is associated with an increased risk for many health-related problems (Hall & Solowij, 1998). Regular use, defined as “every day or almost every day” (Hall & Dagenhardt, 2009), amongst the general population is also known to contribute to
respiratory ailments like chronic obstructive pulmonary disease (COPD), and an increased risk for heart attack or chest pain in patients who already have heart disease (Hall & Dagenhardt, 2009). In addition, individuals who consume cannabis regularly have also been reported to experience short term memory and learning impairments and comorbid mental health conditions such as depression and anxiety (Hall & Solowij, 1998).

Although the literature suggests that cannabis is a risk factor to the early onset of schizophrenia (Moore et al., 2007; Semple et al., 2005; Smit, Bolier & Cuijpers, 2004), it further suggests that cannabis consumption alone may not necessarily be a sole causative factor. This belief is founded on the observation that some youth who go on to develop schizophrenia may never have used cannabis, and alternately, those who consume the drug may never end up developing schizophrenia (Arsenault et al., 2004; Ho et al., 2011). Therefore it is likely, that cannabis is not the single causative factor, but rather it may mediate (i.e., explain how or why a relationship occurs between the independent and the outcome variables) or moderate (i.e., influence the direction and strength of another variable) the onset of schizophrenia in conjunction with other variables (Kraemer et al., 2001).

With respect to the relationship between cannabis use and schizophrenia there is another hypothesis which researchers have considered for explaining this co-occurrence, and that is the self-medication hypothesis. This hypothesis suggests that teens may start using cannabis as a means to manage symptoms of schizophrenia or perhaps even side effects from medications, rather than cannabis causing an expression of the disorder (Smit, Bolier & Cuijpers, 2004). However, several prospective studies refute this hypothesis, contending that cannabis use is a precursor to the disorder (Smit, Bolier & Cuijpers, 2004). All things considered, however, it is clear that more extensive research is required to more fully
understand pathways of association between and among these variables and their impact on the development of this disease.

2.4 Genetics and Epigenetics

As mentioned, genetics is also thought to be a significant risk factor to the early onset of schizophrenia (Caspi et al., 2005; Maki et al., 2011; Vereczkei & Mirnics, 2011), and genetic predisposition combined with environmental risk factors (i.e., cannabis use) can amplify this risk. Genetic links to schizophrenia have been viewed both broadly (i.e., having a familial connection to the disorder) and narrowly (i.e., possessing a specific gene mutation which is thought to be responsible for the disorder). For example, it is considered that the closer the family member is to an individual who has the disorder, such as with identical twins, the greater the risk for developing the disorder. Much effort over the last few years has been invested into genetic studies of schizophrenia, attempting to identify specific genes which may increase risk (Gilmore, 2010).

Numerous susceptibility genes have been considered to be responsible for the onset of schizophrenia. The one particular gene that has sparked interest over the last decade, is the catechol-O-methyltransferase (COMT) gene (Casadio et al., 2011; Caspi et al., 2005; Henquet, Di Forti, Morrison, Kuepper, & Murray, 2008). The COMT gene is of particular interest because it is involved in the metabolism of dopamine that is released into synapses, and disturbances in dopaminergic function are implicated in the pathogenesis of schizophrenia (Caspi et al., 2005). Of interest, it is thought that a functional polymorphism in this gene (Val158Met) may heighten the risk for developing schizophrenia, particularly in those who use cannabis. Genetic polymorphism is defined as “the inheritance of a trait controlled by a single genetic locus with two alleles” (Abraham & Adithan, 2001, p. 147).
Valine (Val) and methionine (Met) are the two COMT alleles that have been studied with respect to this functional polymorphism. Recent findings show that adolescent cannabis use is associated with an increased risk of schizophrenia among Val/Val individuals and, to a lesser extent, among Val/Met individuals, but not among Met/Met individuals (Casadio et al., 2011; Caspi et al., 2005; Henquet et al., 2008).

However, although susceptibility genes are believed to increase the risk for the development of schizophrenia, it is also recognized that not all individuals who are genetically predisposed to developing schizophrenia will go on to develop the disorder (Riley & Kendler, 2006). This understanding lends support to the belief that schizophrenia results from not only individual risk factors, but from a combination of both individual and environmental risk factors as well (phenotype). For example, this line of inquiry has been explored using twin studies, identifying monozygotic (identical) twins as having a heritability of approximately 80-86% for development of the disorder (Tsuang et al., 2001; Riley & Kendler, 2006). Taken together, the preceding findings suggest that although schizophrenia may be largely genetically mediated, it is not genetically determined (Riley & Kendler, 2006).

2.5 Endocannabinoid System

The last few years have witnessed a heightened interest in understanding the role of the endocannabinoid system. This system which was discovered in the late 1980’s and early 1990’s (Hill, 2014) is believed to play a significant role in the relationship between cannabis use and early onset of schizophrenia in those who consume cannabis heavily during adolescence. The endocannabinoid, or endogenous, cannabinoid system is an internal biological system that is responsible for bioregulation or the maintenance of homeostasis.
(Griffing, 2013; Pertwee, 2008; Sulak, 2014). It is a unique communications system that is comprised of both endocannabinoids and their receptors (CB1 and CB2) and is believed to affect many important functions such as how a person feels, moves, and reacts (Sulak, 2014).

CB1 and CB2 receptors are located throughout the brain and body. CB1 receptors are most abundant in the central nervous system (CNS) (i.e., the brain and spinal cord) but they also sparsely populate other parts of the human body. CB2 receptors tend to be located peripherally and in organs, and in cells associated with the immune system (Chaperon & Thiebot, 1999; Pertwee, 2008; Sulak, 2014). Receptors act like a lock-and-key, responding to the “signals” of cannabinoids. The endocannabinoid system is believed to mature slowly and reach maximal levels during adolescence, but is then reduced later in life as a result of post-adolescent neural pruning (Behan et al., 2012).

The two most common endogenous cannabinoids that are produced by the body are anandamide and 2-arachidonoylglycerol (2-AG). These endocannabinoids are found primarily in the CNS and have an affinity for binding to CB1 receptors. Anandamide and 2-AG serve as retrograde signaling messengers in GABAergic and glutamatergic synapses, and are modulators of postsynaptic transmission, interacting with neurotransmitters such as dopamine (Rodriguez de Fonseca, Del Arco, Bermudez-Silva, Bilbao, Cippitelli & Navarro, 2005). Unlike other neurotransmitters, endocannabinoids work backward to the presynaptic neuron and attach to cannabinoid receptors. And because endocannabinoids act on presynaptic cells, they do not control what happens after these cells are activated; thus affecting how messages are sent, received, and processed by the cell.

During adolescence the endocannabinoid system, like other systems, is continually developing. This system is believed to be instrumental for “cortical development, neuronal
migration, connectivity and synaptogenesis” (Hill, 2014, p. 76). Interestingly, it is very rich in cannabinoid receptors and is a region that tends to be most affected by schizophrenia (Hill, 2014). The endocannabinoid system during adolescence undergoes dramatic changes to CB1 receptors (i.e., they increase from early life, peak just at the onset of adolescence, and then subsequently decline afterward and throughout aging) (Hill, 2014). It is suggested that any disruption to this area of the brain during epoch of maturation (i.e., via the introduction of exogenous cannabinoids) may adversely impact both the morphology and the function of this brain area (Hill, 2014). What this means is that cannabis would confer more deleterious effects on the developing brain during adolescence than it would on a mature adult brain (Hill, 2014).

In summary, this overview of the literature provides background on cannabis and several underlying biological mechanisms and environmental risk factors that may contribute to early onset schizophrenia in teens with history of heavy cannabis use. However, because the various factors and pathways of association have been studied in isolation of each other, it is important to provide a summary and synthesis of findings across existing studies. From this review of literature I have identified several key variables. This served to distinguish the inclusion and exclusion criteria, as well as several keywords for this systematic review to help identify contributory factors from the relevant literatures.

To reiterate, the purpose of this thesis is to conduct a systematic review (SR) of current evidence to identify factors that have been reported to be associated with the development of schizophrenia in adolescents who consume cannabis heavily. To locate eligible studies I sought to answer the following researchable question “What are the risk
factors associated with the development of schizophrenia in adolescents who consume cannabis daily?”
Chapter 3: Methods

This chapter provides a summary of the systematic steps I took to conduct my systematic review (SR) to answer my PICO formulated question. I begin with a description of the methods I used to carry out the search (inclusion and exclusion criteria and key terms used), then follow with an explanation of how I aimed to minimize bias through intra rater reliability. I then provide an explanation of how I constructed the matrix tables (i.e., the organization, data extraction and synthesis), the instruments that were used to critically appraise the methodological quality (strengths/weaknesses) of studies.

3.1 Methodological Approach

To answer my question and to conduct my SR, I primarily drew on Garrard’s method of SR (2011). This enabled me to systematically locate, organize and appraise relevant studies. This method is considered a credible and systematic approach for identifying relevant literature, organising and critically evaluating it, as well as synthesising and incorporating findings across studies (Klopper et al., 2007). It was beyond the purpose of this thesis to have performed a meta-analysis.

3.1.1 Search strategy for identifying relevant studies.

To locate relevant studies, the systematic search process involved establishing predetermined inclusion and exclusion criteria followed by systematic search of each of the following nine electronic health data bases: Google Scholar, the Cochrane Central Register of Controlled Trials (via Cochrane Library) and the Cochrane Database of Systematic Reviews (via Cochrane Library), the Database of Abstracts of Reviews of Effects (DARE), PUBMED, MEDLINE, EMBASE, CINAHL, and then PsycINFO. I further searched reference lists of eligible studies to locate additional relevant studies. The titles and abstracts
from located studies were checked against the predetermined inclusion and exclusion criteria to determine their eligibility and relevance to this systematic review.

3.1.2 Inclusion and exclusion criteria.

To be included in this SR, studies had to answer my PICO question and had to be written in the English language. The studies also had to include samples of adolescents, between 10 years and 19 years of age, with a documented history of consuming cannabis daily and who were formally diagnosed as having schizophrenia, schizoaffective disorder, and delusional disorders using DSM-IV criteria or who were assessed as exhibiting symptoms of psychosis. I included these different kinds of diagnoses to broaden my search and because they are closely related to schizophrenia and are often used as inclusion criteria in studies that examine schizophrenia during adolescence.

The types of research studies that were included had to be primary observational studies such as cohort (longitudinal, retrospective), cross-sectional, and case control studies that examined association between various factors and early onset schizophrenia. As described by Polit and Beck (2012), longitudinal cohort studies are those studies that occur over an extended period of time and where data are collected during more than one time point. Longitudinal studies are appropriate for studying a particular phenomenon over time to see changes or outcomes that either happen over time, or take a longer time to emerge. These studies were chosen for this SR as the emergence of psychotic illness can take several years to present, but it is also helpful when trying to understand the temporal order of events (Polit & Beck, 2012). Retrospective cohort studies, which, also defined by Polit and Beck, start with the manifestation of the outcome and then search for a potential cause. Although not as strong as the longitudinal study, this type of design would be appropriate when
looking back at previous patterns of cannabis use or history of psychotic illness.

Retrospective studies are often cross-sectional with data on both the independent and dependent variable being collected during one time point in time (Polit & Beck, 2012). This type of study was chosen as it is a good type of study to examine the relationship among phenomena, but during a fixed point in time. Lastly, case-control studies were also chosen to examine in this SR. Case-control studies examine both cases and control groups within a particular point in time to look for differences between them (Polit & Beck, 2012). The ‘case’ in this instance would be the person who has schizophrenia. All of these designs were chosen for their ability to describe or find associations and relationships between risk factors and symptoms of schizophrenia.

I excluded studies that did not meet inclusion criteria and that examined outcomes not inclusive of schizophrenia and studies in which the adolescent study population had pre-existing brain impairment due to organic causes, as well as studies that did not include the consumption of cannabis. I also excluded papers that were non-studies such as opinion papers and government reports.

3.1.3 Key terms.

Each of the nine health electronic databases was systematically searched using key words and phrases related to the PICO question and that had been identified from the literature overview. These key words or combinations of included: Adolescent, Teen, Brain/Neuro Development, Vulnerability, Risk, Cannabis use, Marijuana use, Substance Use, Drug use, Pot use, THC, Endocannabinoid system, Epigenetics or Genetics, Psychotogenic effects of…, contributes to…, the onset of…, greater risk for…Psychosis, Schizophrenia, Psychotic break, etc. To broaden the search in the electronic databases truncation, thesaurus,
and wildcard strategies were also used. Additionally, I made use of terms such as ‘AND’, ‘OR’, or ‘NOT’ (aka Boolean operators) to expand or narrow down the results.

The systematic search yielded a total of 42 studies. Of the 42 studies located, 10 were excluded at the first phase for the following reasons: they were not primary studies (n=1); they did not answer the PICO question (n=6); and they did not address schizophrenia or long term psychosis (n=3). During the second phase, my supervisor and I also excluded 16 studies: studies that used animals rather than human subjects (n=2); studies that described psychosis as being transient, related to other medical conditions, or as a result of acute intoxication (n=1); studies that looked at alcohol use concurrently (n=1); studies that used a population outside of the inclusion criteria (i.e. majority were adults or young adults and not adolescents) (n=11); and studies that did not use a formal diagnostic tool (n=1). The ultimate selection included 16 studies. These 16 studies met the specified inclusion criteria and were retained based on consensus agreement with my supervisor using intra-rater reliability procedures (described below).

3.1.4 Intra-rater reliability.

The ultimate selection of studies was based on intra-rater reliability testing to calculate the percentage agreement of my initial selection of studies and selection of studies approximately two weeks later using a Cohen’s κ coefficient (κ = .80). This step was taken to provide confidence that the search strategy is replicable and to minimize the risk of potential reviewer selection bias. Percentage agreement scores between my first and second ratings of selection that reached κ=.80 were retained. Next, my supervisor and I discussed any discrepancies and came to consensus on the studies to ultimately retain making use of
inclusion criteria (Kottner et al., 2011). This process resulted in discarding 26 studies and retaining a final listing of 16 studies that composed this review.

3.1.5 Construction of the matrix tables.

To facilitate subsequent extraction and synthesis, data from the 16 studies were organized and structured into four separate matrix tables as per the Garrard (2011) method. The Garrard method is both a structure and a process for systematically organizing, extracting and synthesizing data from studies for a SR. Information from studies are displayed and structured into a matrix table with column and rows so that relevant information and data from each of the retained studies could be compared and contrasted (Garrard, 2011). In this SR four matrix tables (see the four tables grouped together at the end of the thesis) were constructed according to the specific category or factor that was examined. For example, Table 1 consisted of seven studies that addressed ‘Cannabis use in adolescence as a risk factor for psychotic illness’; Table 2 included five studies that examined the ‘Impact of adolescent cannabis use on neurodevelopment’; Table 3 had one study which explored ‘How genetics/epigenetics relate to the onset of psychosis in adolescents who use cannabis’ and Table 4 consisted of three studies that considered ‘Childhood trauma as a risk factor for psychotic symptoms in adolescents who use cannabis’. Each table consisted of rows which listed studies according to the specific category or factor. None of the 16 studies were listed in more than one table.

Each of the four tables was further structured to include 9 columns that contained major headings. The major headings of columns included ‘Author and Year’ of the study, ‘Study Design & Objective’, ‘Sample Size/Method and Study Groups’, ‘Variables (Independent, Dependent, Confounders)’, ‘Tools & Diagnostic Assessment Approach’, ‘Data
Collection/Time Points & Data Analysis’, ‘Internal/External Validity and Strengths/Weaknesses’, ‘Main Findings/Conclusions’, and lastly, ‘Author Recommendations’ and ‘Main Contributions’ of the study. These column headings were chosen because they were appropriate for the types of studies I anticipated including in the SR.

3.1.5.1 Organization, data extraction, and synthesis.

To organize data, the 16 studies were entered in chronological order (later date to most recent date of publication) into the rows of their respective tables. I then populated data from each respective study in summary form into each of the 10 columns. The entire process led to the development of four completed matrix tables (again, see the four tables grouped together at the end of the thesis).

This matrix table format, with each of the four tables having same major column headings enabled me to identify various risk factors within each table grouping and across the tables. It also enabled me to compare and contrast all of the studies in the SR to clearly identify similarities and differences between studies within groups and amongst all of the groups as a whole. From this, I was able to extract and synthesize findings of the 16 studies to identify strengths and limitations, and to comment on existing gaps and current state of the evidence from the studies that were included.

3.2 Critical Appraisal of Study Methodology

After all of the data were extracted and synthesized from each of the four tables, I critically appraised data for reporting and methodological quality. Methodological strengths and limitations of each individual study where examined within each of the matrix categories/groups according to type of study design making use of the ‘Strengthening the
reporting of observational studies in epidemiology’ (STROBE) checklist tool (see below). As per inclusion criteria, the specific types of observational studies that were appraised consisted of cohort studies, cross sectional studies, and case control studies.

3.2.1 Instrumentation.

The STROBE checklist (see Appendix A) tool was developed by a consortium of methodologists, researchers and journal editors (Vandenbroucke et al., 2007; von Elm et al., 2008). It serves as a standardized resource for reviewers to assess methodological quality of observation studies in papers they are reviewing, and in turn for researchers to improve the methodological quality and reporting of observational studies. Currently, the STROBE tool has been adopted by editors of leading journals worldwide (von Elm et al., 2008).

One of the reasons I opted to use this tool because it was directly and freely accessible from the STROBE-statement website (STROBE-statement, 2014) and I found it easy to interpret and to apply. However, despite its accessibility and ease of use, the main reason for choosing the STROBE tool was because it has been successfully used to appraise the thoroughness of the reporting of specific types of study designs such as those studies included in this review (cohort studies, case-control studies, and cross-sectional studies)(Vandenbrouke et al., 2007). Poor reporting is considered to interfere with the assessment of the strengths and weaknesses of a study and the generalizability of its results (Vandenbrouke et al., 2007). In my selection of study instruments, I decided against adding a tool for assessing methodological quality and that would generate a summary numeric of quality. I did this because I wanted to provide a detailed narrative of the methodological strengths and the limitations of each of the studies, rather than reporting a numerical summary score of the quality of studies combined. Currently, there is no gold standard, nor
is there consensus regarding the most appropriate critical appraisal tool (Katrak, Bialocerkowski, Massy-Westropp, Kumar & Grimmer, 2004). However, there is agreement that reporting a numerical score of study quality is of limited value. According to Katikureddi, Egan & Petticrew (2014), the Cochrane Collaboration is emphasizing a move away from rigid checklists and scores to instead recommending a detailed narrative description of methodological strengths and limitations to better help communicate the overall state of the existing science and to make explicit gaps in research requiring attention.

As can be seen in Appendix A, the STROBE checklist consists of 22 items. Of the 22 items, 18 are general items for appraising the internal and external validity of cohort studies, case-control studies, and cross-sectional studies and 4 are specific items for assessing each of the three study designs individually (Vandenbroucke et al., 2007; von Elm et al., 2008). For example, questions 8, 13, 14, and 15 (see Appendix A: STROBE Statement—checklist of items that should be included in reports of observational studies) require additional information for both cases and controls in the case-control studies, and, if applicable, for the exposed and unexposed groups in the cohort and cross-sectional studies (Vandenbroucke et al., 2007). The items on the entire checklist relate to the title, abstract, introduction, methods, results and discussion sections. Examples of specific items for appraising internal and external validity include: examining efforts to limit bias and adjusting for confounders, how the sample was chosen and how the sample size was achieved, as well as overall generalizability of the study findings, etc.

It is important to note that although the STROBE checklist was developed to ensure complete reporting in observational studies submitted for peer review, the checklists have been used effectively by Bastuji-Garin et al. (2013) to evaluate the quality of study
methodology. For example, Bastuji-Garin et al. (2013) first abstracted the 22 items of the STROBE checklist by answering 57 questions adapted from those used by Langan et al. (2010). From this, the authors developed four standard response categories to score each of the 57 questions (i.e., ‘yes’, ‘in part or unclear’, ‘no’, and ‘not applicable’) from which a total percentage score of quality was calculated (the number of the 22 STROBE items adequately reported divided by the number of applicable items x 100) (Bastuji-Garin et al., 2013).

3.2.2 Assessment of methodological quality.

To conduct my critical appraisal of the 16 studies included in my SR, I began by developing a table and, similarly to Bastuji-Garin et al. (2013), I determined whether or not the studies met the criteria from each of the 22 items on the checklist by identifying one of four responses in each area (i.e. Y=Yes, N=No, IC=Incomplete, and (-) = Not Applicable) (see Appendix B for an examination of studies based on STROBE Statement Checklist). From this I was able to further my synthesis and to provide a discussion of individual methodological strengths or shortcomings from each study included in this SR.

3.3 Synthesis of Study Findings

Data extracted from the varying columns of the matrices, including a critical analysis of methodology quality (strengths and limitations), are synthesized and presented in the Result chapter in the form of an integrated narrative synthesis and in the respective tables as appropriate.
Chapter 4: Results

In this chapter I provide a synthesis of the study characteristics, main findings and methodological quality of the 16 studies contained in this SR. This was to help identify how the studies answered my PICO question and to identify similarities, differences and gaps. To do this, I first present my findings by table groupings followed by a presentation of the 16 studies taken together. Please see the four tables grouped together at the end of this thesis (Table 1: Cannabis use in adolescence as a risk factor for psychotic illness, Table 2: Impact of adolescent cannabis use on neurodevelopment, Table 3: How genetics/epigenetics relate to the onset of psychosis in adolescents who use cannabis and Table 4: Childhood trauma as a risk factor for psychotic symptoms in adolescents who use cannabis) for greater detail within each of the respective table groupings.

4.1 Study Characteristics by Study Table

4.1.1 Table 1: Cannabis use in adolescence as a risk factor for psychotic illness.

Table 1 consisted of seven large epidemiological studies on the topic of cannabis use in adolescence as a risk factor for psychotic illness: Andreasson, Engstrom, Allebeck, & Rydberg, 1987; Arseneault et al., 2002; Ferdinand et al., 2005; Henquet et al., 2004; Manrique-Garcia, Zammit, Hemmingsson, Andreasson, & Allebeck 2011; Stephanis et al., 2013; Zammit et al., 2002.

4.1.1.1 Study aim and study design.

All seven studies were specifically aimed to examine whether or not cannabis use during adolescence is a risk factor for future psychotic symptoms. In addition, one study (Henquet et al., 2004) sought to examine the risk in those with an above average predisposition (i.e. genetic predisposition), another (Ferdinand et al., 2005) examined the
trend in risk over time in the general population, and a third (Stephanis et al., 2013) examined whether or not there was a temporal association between age at initiation of cannabis use and the age at onset of psychotic illness.

The seven studies used various cohort study designs including longitudinal or prospective (Andreasson et al., 1987; Arseneault et al., 2002; Henquet et al., 2004), retrospective (Manrique-Garcia et al., 2011; Stephanis et al., 2013), both retrospective and prospective together (Ferdinand et al., 2005), as well as historical (Zammit et al., 2002). Of the seven studies, two (Garcia et al. 2011; Zammit et al. 2002) reported on continuation of the earlier study by Andreasson et al. (1987) by extending the follow up period to identify additional cases. Arsenault et al. (2002) also performed a secondary analysis of data from a previous general population health study (Silva & Stanton, 1996) to examine trend and development of psychiatric outcomes specific to adolescent use of illicit substances, and childhood psychotic symptoms.

4.1.1.2 Sampling approach and sample size.

The primary sampling methods amongst this group of studies were convenience sampling (Andreasson et al., 1987; Manrique-Garcia et. al, 2011; Zammit et al., 2002) or random selection from existing population databases (Ferdinand et al., 2005; Henquet et al., 2004; Stephanis et al., 2013). The study sample size ranged from 759 to just over 40,000 (Andreasson et al., 1987; Manrique-Garcia et al., 2011; Zammit et al., 2002).

4.1.1.3 Study sample characteristics.

Of the seven studies, three consisted of only male subjects that were obtained from the Swedish military registry (Andreasson et al., 1987; Manrique-Garcia et. al, 2011; Zammit et al., 2002). Only two had an equal, representative number of both male and female subjects.
(Ferdinand et al., 2005; Henquet et al., 2004) while the remaining did not report on the
gender breakdown (Arsenault et al., 2002; Stephanis et al., 2013). However, the Arsenault et
al. (2002) study may not have reported on gender because that study was a secondary
analysis of data from the earlier study (Dunedin multidisciplinary health and development
study) by Silva & Stanton (1996) that had reported on gender.

4.1.1.4 **Main study independent variable.**

Across the seven studies, cannabis use was the main independent variable. Although
cannabis use was defined as any form of cannabis consumption, some studies additionally
assessed frequency of cannabis use (Arsenault et al., 2002; Andreasson et al., 1987; Henquet
et al., 2004; Manrique-Garcia et al., 2011; Zammit et al., 2002) and age at which cannabis
was first used (Arsenault et al., 2002; Stephanis et al., 2013).

4.1.1.5 **Main study outcome variable.**

In all of the seven studies, schizophrenia or chronic long term psychosis in
adolescence was identified as the main study outcome although the studies varied in how this
main outcome was defined. For example, investigators included youth who exhibited both
symptoms of schizophrenia and depression (Arsenault et al., 2002) or a diagnose of
schizophreniform disorder and depression (Arsenault et al., 2002); schizophrenia and other
psychoses (Zammit et al., 2002); psychotic symptoms (Ferdinand et al., 2005; Henquet et al.,
2004); and schizophrenia and other non-affective psychoses (Manrique-Garcia et al., 2011).
Moreover, the study by Stephanis et al. (2013) also considered the age at which psychosis
first occurred as the outcome.
5.1.1.6 Intervening or confounding variables.

Five of the seven studies controlled for drug use other than cannabis use such as tobacco, narcotics, cocaine, solvent use, amphetamine, alcohol, etc. to control for confounders which may also account for the outcome (Andreasson et al., 1987; Arsenault et al. 2002; Henquet et al., 2004; Stephanis et al., 2013; Zammit et al., 2002). The early study by Andreasson et al. (1987) also controlled for contact with police, running away from home, fathers’ alcohol habits, school adjustment, socioeconomic group, psychiatric diagnosis at conscription, and medication for nervous problems or family member on medication for nervous problems. Arsenault et al. (2002) also controlled for psychotic symptoms at 11 years (at baseline) and depressive symptoms (at 26 years).

Other variables that were controlled for included psychiatric diagnosis at conscription (Manrique-Garcia et al., 2011; Zammit et al., 2002) predisposition for psychosis (Henquet et al., 2004), family history of psychiatric illness (Zammit et al., 2002), history of childhood trauma (Henquet et al., 2004), personality traits and personality variables concerned with interpersonal relationships (Zammit et al., 2002), disturbed behaviour in childhood (Manrique-Garcia et al., 2011; Zammit et al., 2002), IQ, (Manrique-Garcia et al., 2011; Zammit et al., 2002) as well as place of upbringing (i.e. urbanicity/in a city) (Andreasson et al., 1987; Henquet et al., 2004; Manrique-Garcia et al., 2011). Interestingly, some studies included paternal age as a study variable, as advancing paternal age has been shown to be a risk factor for schizophrenia (Zammit et al., 2002). Additional study variables included the financial situation of the family, (Henquet et al., 2004; Zammit et al., 2002) as well as the father’s occupation (Zammit et al., 2002). Additionally, two studies controlled for sex (Ferdinand et al., 2005) and age (Ferdinand et al., 2005; Henquet et al., 2004).
4.1.1.7  **Study tools and data collection.**

Data were collected using questionnaires or self-reports to obtain information about upbringing, school and personal relationships, use of cannabis or other narcotics and alcohol (Andreasson et al., 1987; Arsenault et al., 2002; Manrique-Garcia et al., 2011; Zammit et al., 2002). Authors also made use of valid and reliable diagnostic tools and structured interviews with trained qualified clinicians to confirm diagnoses. There tools included the ICD (International Classification of Diseases) version 8 (Andreasson et al., 1987; Manrique-Garcia et al., 2011; Zammit et al., 2002), ICD version 9 and 10 (Manrique-Garcia et al., 2011), DSM-4 (Diagnostic and Statistical Manual of Mental Disorders) (Arsenault et al, 2002), the CIDI (Composite International Diagnostic Interview) (Ferdinand et al., 2005; Henquet et al., 2004), and the DIP (Diagnostic Interview for Psychosis) (Stephanis et al., 2013). The Munich version of the CIDI was used by Henquet et al., and the Swedish version of the ICD was used by Manrique-Garcia et al. Data was also collected by obtaining IQ scores (Manrique-Garcia et al., 2011), conducting surveys (Stephanis et al., 2013), or performing face to face interviews using computerized assisted methods (Henquet et al., 2004).

4.1.1.8  **Time points of data collection.**

In the prospective longitudinal studies, data were collected at various time points. Andreasson et al. (1987), for example, followed subjects over a 15 year time block and obtained data using the national registry; Ferdinand et al. (2005) followed subjects from 1981-1997 and collected data at six different points in time; and Arsenault et al. (2002) collected data on subjects when they were 15 years (baseline), 18 years, and then at 26 years of age. Henquet et al. (2004) conducted their study over four years, where they collected data.
data at baseline and then at follow up. The three other studies, i.e., those that used retrospective designs (Manrique-Garcia et al., 2011; Stephanis et al., 2013; Zammit et al., 2002), collected data only once.

Ages of subjects within the studies tended to depend on the type of study design that was used. For example, prospective cohort studies enrolled subjects at a younger age and then followed them over several years, whereas retrospective studies enrolled subjects who were adults but collected data from subjects’ past, during their adolescence. The three Swedish military conscript studies (Andreasson et al., 1987; Manrique-Garcia et al., 2011; Zammit et al., 2002) initially examined study participants at ages 18 and 19 years, but then made use of a national registry to observe outcomes into adulthood 15 years later (Andreasson et al., 1987), 27 years later (Zammit et al., 2002), and 35 years later (Manrique-Garcia et al., 2011). Similarly, Arsenault et al. (2002) obtained baseline data from study participants when they were 15 and 18 years of age but then assessed for psychiatric symptoms at age 26. Ferdinand et al. (2005) obtained baseline data between the ages of 4-16 years over six different points in time with the 6th last data collection occurring when participants were between the ages of 18-30 years of age. Henquet et al. (2004) collected data over four years from adolescents aged 14-24 years; and alternately, Stephanis et al. (2013) collected data from a broader population of 18-64 year olds, but assessed for age at first cannabis use and onset of psychosis retrospectively.

4.1.1.9 Methods of data analysis.

Data were analyzed using logistic regression (Andreasson et al., 1987; Henquet et al., 2004; Manrique-Garcia et al., 2011; Zammit et al., 2002), multiple linear regression (Arsenault et al., 2002), univariate linear models (Stephanis et al., 2013), and cox regression
and or hazard ratio (Ferdinand et al., 2005; Manrique-Garcia et al., 2011; Zammit et al., 2002). These methods were used to examine and or predict the relationship between variables (cannabis use and psychotic symptoms). Cox regression is used to predict outcomes over time and hazard ratios are calculated to determine the rate at which events happen. Both of these statistics help to make predictions, and account for death and for drop outs along the way which are common occurrences in long term follow-up studies (Polit & Beck, 2012).

**4.1.1.10 Main study findings.**

The main finding of seven studies taken together was that cannabis use during adolescence was significantly associated with the early onset of schizophrenia and symptoms of schizophrenia during adolescence and early adulthood. The Andreasson et al. (1987) was the first to report on this line of evidence.

In their analysis of 45,570 Swedish military conscripts, Andreasson et al. (1987) showed a relative risk (RR) of 6.0 (95% CI 4.0-8.9) for developing schizophrenia in heavy cannabis users (those who used cannabis 50 times or more in a lifetime) compared with non-users. Analysis of data showed that the greater the frequency of use and the greater the amount of cannabis consumed, the greater the risk for the development of psychotic disorders, in what authors described as a dose-response relationship (Henquet et al., 2004; Zammit et al., 2002). The findings were further supported by Zammit et al. and most recently by Manrique-Garcia et al. (2011) who carried out two subsequent studies that built upon and followed up on the same cohort from the original Andreasson et al. study. Zammit and colleagues also found that early and heavy cannabis users were 6 times more likely to develop schizophrenia, (adjusted OR 6.7 (95% CI, 2.1 to 21.7)). In that study, extended
analysis further showed that those who consumed cannabis more than 50 times in their lifetime were at greatest risk for the onset of schizophrenia, and that this association was not accounted for by use of other psychoactive drugs, personality traits or other psychological symptoms (Zammit et al., 2002). In their study, Manrique-Garcia et al. showed those who frequently use cannabis were three times more likely to develop brief psychotic outcomes, (OR 3.7 [95% CI, 2.3–5.8] twice as likely to develop schizophrenia (OR 2.2 [95% CI 1.0–4.7] and twice as likely to develop other non-affective psychoses (OR 2.0 [95% CI 0.8–4.7]) compared with those who do not use cannabis.

Arsenault et al. (2002) also found that there was an inverse relationship between age of starting using cannabis and the risk of schizophrenia, meaning that the younger someone was when they first started using cannabis, the greater the risk for developing schizophreniform disorder or schizophrenia symptoms at age 26 compared to controls. In that study, the risk for adult schizophreniform disorder continued to remain high even when childhood psychiatric symptoms were controlled for in the analysis.

Most recently, Stephanis et al. (2013) provided further evidence that age at first cannabis use was directly and linearly associated with age at first psychosis, but that there seemed to be an average delay of 7–8 years (mean 7.85, SD = 6.2) from the first exposure to cannabis to the first psychosis. These results remained consistent even after family history of schizophrenia or other psychiatric disorders was included as a covariate, F (11, 984) = 13.77, P < .001, R^2 = 0.20. They support findings of an earlier study conducted by Ferdinand et al. (2005) that reported a 7.8 year interval between initial use of cannabis and the presentation of symptoms of schizophrenia. However, their findings may not necessarily support a neurodevelopmental “window of vulnerability” hypothesis because they found a similar
temporal trajectory between subjects who first used cannabis at 12 years of age and at 19 years of age. Rather, the authors argue that cannabis could be exerting a cumulative toxic effect to an individual’s pathway to developing psychosis (Stephanis et al., 2013).

Some of the studies within this group showed that although cannabis use in young people is a risk factor for the onset of schizophrenia, the risk may be more due to predisposition to develop the disease rather than due to the self-medication hypothesis. Henquet et al. (2004), for example, suggest that those who are predisposed to psychosis have a greater risk for psychotic symptoms if they use cannabis during adolescence or young adulthood than those who are not predisposed. These authors also found that an increased predisposition for psychosis at baseline did not significantly predict cannabis use which may refute the self-medication hypothesis.

4.1.2 Table 2: Impact of adolescent cannabis use on neurodevelopment.

Five studies were included on the topic of the impact of cannabis use on neurodevelopment during adolescence (James et al., 2011; Peters et al., 2009; Cohen et al., 2012; Kumra et al., 2012; Solowij, Youcel, Respondek, Whittle, & Lindsay, 2011).

4.1.2.1 Study aims and study design.

All five studies were aimed to assess the impact of cannabis use on neurodevelopment during adolescence. All made use of magnetic resonance imaging (MRI) to obtain images of the brain for comparison amongst subjects and controls. The MRI is considered a valid and reliable approach for obtaining objective data related to brain structure and function. Of the five, two were case-control studies (James et al., 2011; Peters et al., 2009) and remaining three were cross-sectional (Cohen et al., 2012; Kumra et al., 2012; Solowij et al., 2011). The Peters et al. case control study examined recent onset
schizophrenia patients who used and did not use cannabis, comparing them with matched group controls to test the hypothesis that cannabis use during early adolescence is associated with white matter abnormalities in schizophrenia patients. Similarly, the case control study by James and colleagues made use of two matched comparison groups to examine cognitive and structural (grey and white matter) changes between patients with adolescent-onset schizophrenia who had history of early cannabis use or not.

Of the three cross-sectional studies, Solowij et al. (2011) examined cerebral grey (GM) and white matter (WM) in cannabis users with and without schizophrenia and Cohen et al. (2012) examined the effect that cannabis use had on cerebellar pathology in young people diagnosed with first episode schizophrenia. Similarly, Kumra et al. (2011) also examined cerebral cortical grey matter structure in adolescents, in regions of interest (ROI) of the brain. In that study, the specific ROI’s that were examined were the left and the right superior parietal cortex, which have consistently been shown to be altered in adolescents with schizophrenia but with no history of substance misuse (Kumra et al., 2011).

4.1.2.2 Sampling approach and sample size.

All five studies made use of convenience sampling with subjects recruited from adolescent inpatient units (James et al., 2011; Peters et al., 2009) or day units (Peters et al., 2009), by referral from a psychiatrist or a research bank (Solowij et al., 2011), and through clinical programs at a university (Kumra et al., 2012). Across the studies the study sample sizes ranged from between N=32 (James et al., 2011) and N=115 (Kumra et al., 2012). Samples were broken down into various subgroups, further reducing each subgroup sample size. The study by Peters et al. consisted of a group of males with recent-onset schizophrenia (with and without a history of cannabis use before 17 years) and a matched group of healthy
males with no history of drug use. James and colleagues compared subjects with adolescent onset schizophrenia (AOS) with and without history of cannabis use. Solowij et al. (2011) compared patients with schizophrenia against a group of healthy controls while Cohen et al. (2012) compared three study groups: healthy controls, young cannabis users, non-users, and cannabis using first episode schizophrenia outpatients. Lastly, the Kumra et al. study compared four groups: subjects with early onset schizophrenia, subjects with cannabis use disorder, subjects with early onset schizophrenia and cannabis use disorder, and a group of healthy controls. Within this sample, early onset schizophrenia subjects (with a reported onset of psychosis prior to 18 years) were broken down into further subgroups of schizophrenia (n =38), schizoaffective disorder (n= 3), and schizophreniform disorder (n =7) (Kumra et al., 2012).

4.1.2.3 **Study sample characteristics.**

Although all five studies focused on the adolescent population, the age range of subjects ranged between 10-21 years (Kumra et al., 2012), and 21-60 years (Solowij et al., 2011). Although Solowij and colleagues used a broader age range the focus on the consumption of cannabis was during childhood through adolescence and into young adulthood (ages 9-32 years). Other than healthy controls, subjects were individuals who had a diagnosis of schizophrenia (James et al., 2011; Peters et al., 2009; Cohen et al., 2012; Kumra et al., 2012; Solowij et al., 2012), schizoaffective disorder (Kumra et al., 2012; Peters et al., 2009) and or schizophreniform disorder (Kumra et al., 2012; Peters et al., 2009).

4.1.2.4 **Main study independent variable.**

The independent variable in all studies was cannabis use during adolescence. Cannabis, again, was defined as any form of cannabis consumption.
4.1.2.5 Main study outcome variable.

The outcome variable amongst this group of studies was any change that might have occurred (or not) in the subject’s brain resulting from cannabis use during adolescence. These changes were observed by using MRI scans to examine brain matter in each subject. Authors examined the effects of early cannabis use on white brain matter (WM) (Peters et al., 2009), grey brain matter (GM) in regions of interest (Kumra et al., 2012), and both WM and GM concurrently (Solowij et al., 2011). James et al. (2011) examined specifically the cognitive and neuro-structural changes that occurred with cannabis use, and Cohen et al. (2012) examined overall, or more general cerebellar pathology.

4.1.2.6 Intervening or confounding variables.

Variables which might otherwise account for the study findings were controlled for via the study design (in four out of the five studies) by making use of matched controls to equate study groups on subject characteristics (Cohen et al., 2012; James et al., 2011; Peters et al., 2009; Solowij et al., 2011), and statistically to rule out the effects of potential confounders such as medications (chlorpromazine (CPZ) equivalents) (James et al., 2011), age, sex and reading scores (Kumra et al., 2012), as well as alcohol and tobacco (Solowij et al., 2011).

4.1.2.7 Study tools and data collection.

All five studies made use of DSM-IV criteria to diagnose for psychiatric illness and drug and alcohol use. The exception was Solowij et al. (2011) who accepted diagnoses as made by referrals from psychiatrists and from the schizophrenia research bank. In addition, Kumra et al. (2012) and James et al. (2011), made use of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version or the
Structured Clinical Interview for DSM-IV Axis I Disorders (SCID). Data on drug and alcohol use history were obtained via interview, medical records and/or drug urine screening. Other tools that were used to collect data on psychiatric measures included intelligence quotient (IQ), the Hamilton depression rating scale, a scale for the assessment of negative symptoms and positive symptoms (SANS/SAPS) and the Positive and Negative Syndrome Scale (PANSS).

4.1.2.8 **Time points of data collection.**

By virtue of the study designs that were used (cross-sectional, case-control) data for all studies were collected at one time point.

4.1.2.9 **Methods of data analysis.**

Data were analysed mainly using correlational methods such as: the General linear model (James et al., 2011; Kumra et al., 2012), the Pearson product-moment correlations (Cohen et al., 2012; Solowij et al., 2011) for normally distributed data, and then Spearman rank order correlations (Kumra et al., 2012; Peters et al., 2009; Solowij et al., 2011) for skewed data. Correlational statistics methods are able to show whether or not, and how strongly, variables are related and the direction of the relationship (Polit & Beck, 2012). ANOVA (analysis of variance) was used in some studies to analyze the differences in study outcome between groups (Cohen et al., 2012; Peters et al., 2009), and MANCOVA (multivariate analysis of covariance) (Kumra et al., 2012) and ANCOVA (analysis of covariance) to examine variation or to compare study groups in terms of study outcome while statistically controlling for potential confounders (James et al., 2011; Kumra et al., 2012; Solowij et al., 2011).
4.1.2.10 **Main study findings.**

Findings from all five studies suggest that individuals who use cannabis during adolescence show significant MRI-based neuro structural changes in both grey and white matter. James et al. (2011) showed that subjects who used cannabis compared with those who did not had grey matter density loss. The authors suggested that this pattern of grey matter density loss amongst those with early onset schizophrenia and history of heavy cannabis use may reflect synaptic pruning and increasing myelination during this period, and that it is likely an exaggeration of normal maturation (James et al., 2011). Cohen et al. (2012) obtained similar results, showing grey matter reduction in three lobules (lobule III: F3, 16= 4.4, p=0.02; lobule IV: F3, 16=4.7, p=0.02; lobule V: F3, 16=4.6, p=0.02). In that study, total lifetime doses of cannabis significantly predicted grey matter reduction in the three lobules (lobule III: b=x0.63, t=x2.6, p=0.02; lobule IV: b=x0.74, t=x3.1, p<0.01; lobule V: b=x0.52, t=x2.2, p<0.05). Cohen et al. further found that cannabis use did not affect total cerebellar volume, white matter or grey matter volumes, or the total grey matter, but that the regional effects of cannabis use on grey matter depended highly on age at onset of use, the years of use, and the accumulated total lifetime doses.

In another study, Kumra et al. (2012), found that in the left superior parietal region, "pure" early onset schizophrenia (EOS) subjects and "pure” cannabis use disorder (CUD) subjects both had smaller gray matter volumes associated with lower surface area compared with healthy controls. Although both groups, EOS as well as CUD, indicated a smaller volume in grey matter, these findings did not reach significance. However, in the comorbid group (EOS+CUD) there was a significant interaction (F48, 60 1.88, p .01) which showed that the effects of cannabis use on brain morphology is most evident in those who also have
EOS. Notably, these findings suggest that cannabis use may moderate the relationship between early onset schizophrenia and cerebral cortical grey matter structure in the left superior parietal lobe (Kumra et al., 2012).

The forth study by Solowij et al. (2011) also showed a significant group difference between subjects who used cannabis or who had schizophrenia compared with healthy controls. In that study, cannabis users had smaller cerebellar white matter volume compared to non-users. The authors also found white-matter volume was 23.9% smaller in healthy cannabis users and 29.7% smaller in schizophrenia patients who used cannabis. The largest effect observed (i.e., the greatest reduction in cerebellar volume relative to healthy controls) was when cannabis use was co-morbid with schizophrenia. Although in that study, the interaction between schizophrenia diagnosis and cannabis use did not reach significance for effect on white matter volume \( [F(1, 38)=1.15, \ p=0.29] \), the main effect of cannabis use (regardless of diagnosis) was highly significant \( [F(1, 38)=7.76, \ p=0.008] \), and the main effect of diagnosis (schizophrenia versus healthy sample regardless of cannabis use) was significant \( [F(1, 38)=4.31, \ p=0.045] \).

Interestingly, Peters et al. (2009) reported different results. Although this study also showed that changes in brain morphology were present in those who consumed cannabis, this study further found that those individuals who use cannabis in adolescence (before the age of 17 years) tended to present with increased white matter (as opposed to decreased white matter), which was absent in subjects without cannabis use before the age of 17 years (Peters et al., 2009). This outcome was the same for subjects both with and without schizophrenia. These findings lead investigators to conclude that cannabis use may reflect neural structural hyper-connectivity. Connectivity is defined by these investigators as “the structural
connection between brain areas that is directly related to the neural communication between these areas”, therefore hyper connectivity would indicate a “more efficient hardwiring” that results in “an increased functional communication”. Based on their findings Peters et al. concluded that individuals with schizophrenia and who have a history of cannabis use perform better on a variety of tasks (i.e., have better cognition early in the illness, have less negative symptoms, less incoherent speech, etc.) than those with schizophrenia who have no history of cannabis use. Unfortunately the investigators could not conclude that cannabis use was solely responsible for these results as there was a great deal of overlap between cannabis use and other illicit drug use. As the findings from this study only partly confirm the hypothesis, these investigators suggest that additional studies be conducted to assess the effect of adolescent cannabis use and other illicit drug use separately on brain white matter in schizophrenia (Peters et al., 2009).

4.1.3 Table 3: How genetics/epigenetics relate to the onset of psychosis in adolescents who use cannabis.

This table includes only one study (Estrada et al., 2011).

4.1.3.1 Study aims and study design.

The study by Estrada et al. (2011) made use of a cross-sectional design to examine whether age at first cannabis use and age at emergence of psychiatric disorders are related, and if so, if such a relationship was modulated by the Val158Met polymorphism in the COMT gene.

4.1.3.2 Sampling approach and sample size.

The sampling approach was convenience sampling, where N=157 psychiatric inpatients were obtained for the study. Of the total sample, there were two separate groups.
One group consisted of n=80 patients with schizophrenia and the other group had n=77 individuals without psychotic disorders who had either affective or conduct disorders (controls). Both groups in the total sample used cannabis.

4.1.3.3 **Study sample characteristics.**

The sample consisted of adolescents, with a mean age of 17.01 years (SD = 3.6). The authors did not specify in their report the percentage of male to females within the sample.

4.1.3.4 **Main study independent variable.**

The independent variable in this study was cannabis use in adolescence as well as genotype. Both groups in this study were questioned about drug use, age at first use, and frequency, and urine drug screens were conducted. Cannabis use was then further broken down into subcategories: i) lifetime cannabis use or non-cannabis use (dichotomous) and ii) age at first cannabis use (continuous). DNA was obtained from both groups as well to determine genotype for each subject.

4.1.3.5 **Main study outcome variable.**

The outcome variable in this study was the onset of psychosis, which was determined based on hospitalization to a psychiatric unit for recent, first illness onset. This was defined as an illness that presented for less than 1 year, and where there was no more than one previous hospitalization (Estrada et al., 2011).

4.1.3.6 **Control variables.**

The control variable in this study was the absence of schizophrenia. The control group consisted of individuals without psychotic disorders who had either affective or conduct disorders but who also used cannabis.
4.1.3.7 **Intervening or confounding variables.**

Confounders that were controlled for in this study included: individuals who were non-Caucasian, or who had medical illnesses that affected the brain, other neurological conditions, and moderate to severe mental retardation. These confounders were controlled for through the design of the study, by having them listed as exclusion criteria.

4.1.3.8 **Study tools and data collection.**

Data regarding diagnoses were obtained first from interviews by experienced psychiatrists and psychologists and then were determined by the criteria outlined in the DSM IV. The age at onset for psychosis was considered to be the age at first psychiatric admission to hospital. Data were also collected on DNA to identify subject allele combinations (Val/Val, Val/Met, Met/Met). DNA testing was performed using both blood and buccal swab samples, both being reliable and well validated methods for analyzing DNA. Information was also collected with respect to drug use, including the age at first use and the use and frequency of use for psycho-active drugs, and urine drug screens were performed to confirm data from interviews.

4.1.3.9 **Time points of data collection.**

Data in this study were collected during one time point, as is typically the case with cross-sectional designs.

4.1.3.10 **Methods of data analysis.**

Statistical analysis in this study was conducted using t-tests to compare the means of continuous variables between the two groups, those with schizophrenia spectrum disorders versus other psychiatric disorders (affective or conduct disorders); chi-squared tests to analyse the distribution of categorical variables between groups; and linear regression (with
age at onset being the dependent variable, and gender and age at first cannabis consumption as the independent variables) for exploring the effect of both gender and age at first consumption on age of onset of psychiatric symptoms and to test the effect of the interaction between age at first cannabis use and COMT Val158Met genotype on the age of onset of psychiatric symptoms.

4.1.3.11 Main study findings.

This study found that the age at which cannabis is first used correlates with the age at which psychiatric disorders will emerge, and similar to findings reported in studies composing the preceding two table groupings (Table 1: Cannabis Use in Adolescence as a Risk Factor for Psychotic Illness; Table 2: Impact of Adolescent Cannabis Use on Neurodevelopment) this study also supports the conclusion that individuals who start using cannabis at an early age are prone to develop earlier onset of psychiatric disorders. Furthermore, this risk is greatly influenced by the interaction between COMT Val158Met genotype (Estrada et al., 2011). This study showed that individuals who are Val/Val genotype carriers have an earlier age of emergence of psychotic disorders than those who are both Val/Met and Met/Met carriers. This finding supports the hypothesis that the COMT Val158Met genotype may modulate the association between cannabis and age at onset of psychotic disorders. Because these results appear to be consistent with findings of the previous studies contained in this review they highlight the importance of brain maturation timing in which exposure to cannabis occurs.
4.1.4 Table 4: Childhood trauma as a risk factor for psychotic symptoms in adolescents who use cannabis.

This table grouping includes three studies (Houston, Murphy, Adamson, Stringer & Shevlin, 2008; Harley, Clarke, Lynch & Arsenault, 2010; Mackie et al., 2013).

4.1.4.1 Study aims and study design.

All three studies within this table examined trauma in childhood as a risk factor to development of psychotic outcomes in adolescents who consume cannabis. All were aimed to examine a possible additive effect of two independent variables (trauma and cannabis use) to determine whether childhood trauma and cannabis use increased the risk of experiencing psychotic symptoms in adolescence beyond that expected if each risk factor were working independently (Harley et al., 2010; Houston et al., 2008). Two studies were population (epidemiologic) cohort studies which used both prospective (Mackie et al., 2013) and retrospective designs (Houston et al., 2008) while the third was a case control (Harley et al., 2010). Houston and colleagues conducted their study as a secondary analysis of data that was conducted from a previous survey (The National Comorbidity Survey) (Kessler, 1994).

4.1.4.2 Sampling approach and sample size.

Subjects were obtained from large, nationally represented community samples (Houston et al., 2008) and geographical catchment areas (Harley et al., 2010). One study recruited subjects from eight secondary schools in the United States within a large geographical area (Mackie et al., 2013), and used a convenience sampling strategy. In contrast, the other two studies used stratified, multistage, area probability sampling (Houston et al., 2008), and stratified random sampling methods (Harley et al., 2010) to obtain subjects.
Study sample sizes ranged from between N=211 (Harley et al., 2010) and N=5877 (Houston et al., 2008).

### 4.1.4.3 Study sample characteristics.

Subjects’ ages were: 15-54 years with a mean age of 32.02 years (SD = 10.59) (Houston et al., 2008); 12-15 years (Harley et al., 2010); and the mean age of subjects in the Mackie et al. (2013) study was 13.6 years. Although Houston and colleagues used a broad age range in their sample, data regarding childhood sexual traumas and cannabis use were obtained retrospectively to identify whether or not the two variables existed in subjects when under the age of 16 years. The Houston et al. sample consisted of an almost equal proportion of males and females (Males 48.1%, Females 51.9%) and the Mackie et al. (2013) sample consisted of 60.9% males and 39.1% females. Harley et al. did not specify the breakdown of male to female subjects.

### 4.1.4.4 Main study independent variable.

In this set of studies, trauma in childhood and cannabis use were the independent variables. Trauma was defined as sexual abuse (Houston et al., 2008), child abuse, exposure to domestic violence, low social class/poor socioeconomic status and family history of mental illness (Harley et al., 2009), as well as bullying by peers (Mackie et al., 2013). Cannabis use, as in the previous three table groupings, considered cannabis use to be any form of cannabis consumption.

### 4.1.4.5 Main study outcome variable.

The outcome variable was psychosis (Houston et al., 2008) or psychotic symptoms (Harley et al., 2010; Mackie et al., 2013), with Mackie et al. (2013) specifically looking at
the outcome as being the onset of psychotic symptoms were transitory experiences became
abnormally persistent.

4.1.4.6 Control variables.

Only one study used controls (Harley et al., 2010), where the control group in this
study was matched for gender and for school.

4.1.4.7 Intervening or confounding variables.

Each study controlled for confounders such as: exposure to childhood sexual abuse
(CSA) and childhood physical abuse (CPA), sex, age, urbanicity, ethnicity, depression,
education, employment, living arrangements (Houston et al., 2008), gender and school
(Harley et al., 2010), and other nonspecific “illicit” drug use (Mackie et al., 2013). Houston
et al. controlled for confounders by doing it in two blocks. For example, they first performed
covariate analyses to control for the above mentioned confounders (sex, age, urbanicity,
ethnicity, depression, education, employment, living arrangements), and then performed a
second block which controlled for the confounding effects of cannabis use (and non-use) in
those under 16 years and sexual trauma, as well as the cannabis use and sexual trauma
interaction to interpret the interaction amongst variables. In Mackie et al. (2013) all
confounders such as demographics, depression, cigarette, alcohol, other illicit drug use and
previous psychotic experiences were adjusted for statistically. As mentioned, Harley et al.
used matching via study design to control for confounders.

4.1.4.8 Study tools and data collection.

The variables in this group of studies were measured and identified using both valid
and reliable diagnostic tools which included: the CIDI to assess for a lifetime prevalence of
non-affective psychosis, information about cannabis use, and information related to
childhood sexual traumas (Houston et al., 2008); the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) and Children’s Depression Inventory (Harley et al., 2010); as well as questions adapted from the Diagnostic Interview Schedule related to psychosis, the depression subscale from the self-report Brief Symptom Inventory, several items from the Reckless Behavior Questionnaire which assessed for frequency of cannabis use and other illicit drug use, as well as the Olweus Bully/Victim Questionnaire (Mackie et al., 2013). All information was gathered through interviews and participant self-reports (Houston et al., 2008; Harley et al., 2010; Mackie et al., 2013), and formal psychiatric diagnoses were obtained from experienced clinicians using the DSM-III (Houston et al., 2008) or DSM-IV criteria (Harley et al., 2010; Mackie et al., 2013).

4.1.4.9 **Time points of data collection.**

Studies varied in how they collected data, with the studies collecting data at single and multiple time periods. For example, Harley et al. (2010) and Houston et al. (2008) both assessed study outcomes at one time point, whereas Mackie et al. (2013), given their longitudinal study design, collected data at five different time points with each separated by six months and over a 24-month time span.

4.1.4.10 **Methods of data analysis.**

Statistical analyses included odds ratio’s (OR’s) (Houston et al., 2008; Harley et al., 2010) and logistic regression analyses (Houston et al., 2008; Harley et al., 2010; Mackie et al., 2013). In Mackie et al. the investigators used multiple nominal logistic regressions to examine “individual differences across trajectory classes in bullying by peers, onset and frequency of cannabis use, demographic variables and confounding variables such as other illicit drug use”. From this analysis authors were able to predict whether or not there may be
any causal association between cannabis use, bullying by peers and subsequent changes in psychotic experiences, and explore whether or not cannabis use or bullying by peers at Time 1 predicted growth in psychotic experiences between and within Time 2 and Time 5. Harley et al. stratified their data into four separate categories for analysis: (1) no exposure to cannabis use or childhood trauma, (2) exposure to cannabis use only, (3) exposure to childhood trauma only, and (4) exposure to both cannabis use and childhood trauma. The OR’s for groups 2, 3 and 4 were then calculated using group 1 as reference group, where the OR’s were used in the standard formula to calculate an interaction contrast ratio, and where the interaction contrast ratio was interpreted as the proportion of disease among those with both risk factors that is attributable to the interaction (Harley et al., 2010). Lastly, Houston et al. conducted their analysis in two blocks, as mentioned previously, to control for confounders but then to examine, using logistic regression, the interaction between cannabis use and sexual trauma.

4.1.4.11 Main study findings.

Findings of the three studies in this grouping provide evidence to show that various childhood traumas increase the risk for the onset of psychotic disorders in adolescence in those that consume cannabis. They add to the findings from several large prospective studies that show an association between cannabis use and psychotic illness or psychotic symptoms in adolescent populations, showing that there may be additional factors that could also account for this interaction.

Harley et al. (2010) claim that cannabis use as well as childhood trauma (physical abuse and sexual abuse, domestic violence, social class and family history of psychiatric illness in a first or second degree relative) is significantly associated with risk of
experiencing psychotic symptoms. The authors found that adolescents who have experienced childhood trauma were almost five times more likely to use cannabis [OR 4.86, 95% confidence interval (CI) 1.63–14.51, p=0.005] than those who had not experienced trauma, and were also five times more likely to develop psychotic symptoms (OR 5.20, 95% CI 1.58–17.13, p=0.007) compared to those who had not. They were also able to show that the interaction between these variables, when they examined both risk factors under an additive model. It showed evidence of a greater than additive interaction between childhood trauma and cannabis use, and that both increased the risk for psychotic symptoms beyond the risk posed by either risk factor alone. However, it is to be noted that of the 211 total sample, childhood trauma was reported in only 24 (11.3%) of participants interviewed, and from that number, only 14 (6.6%) reported experiencing psychotic symptoms (auditory and visual hallucinations). The authors also acknowledged that no study participant received a formal DSM IV diagnosis of a psychotic illness.

Houston et al. (2008) also reported that childhood sexual trauma and cannabis use increased the likelihood of developing psychotic symptoms in adolescence. Similar to Harley et al. (2010) these authors found that the main effects for cannabis and trauma were not significant alone, but that it was the interaction between the two variables that proved to be statistically significant. These investigators further found that the effect for sexual trauma was only statistically significant for those who used cannabis under the age of 16 years (OR = 11.96, 95% CI = 2.10–68.22, P = .01) but not for those who had not used cannabis under the age of 16 years (OR = 1.80, 95% CI = 0.91–3.57, P = .09). This study suggests that there is likely a mediating role of early cannabis use which may increase the strength of the trauma-psychosis relationship. However authors advised additional studies to identify
whether or not there is a different temporal ordering of cannabis use and trauma. This might show different risks for psychosis, which might identify whether or not exposure to a trauma followed by cannabis use (self-medication) and cannabis use followed by trauma produce different likelihoods of psychosis (Houston et al., 2008).

The study by Mackie et al. (2013), examined the relationship between exposure to bullying during childhood, cannabis use and development of psychotic symptoms. In this study the researchers defined trajectories of psychotic experiences with a three-class model where levels of psychotic experiences were reported across five time points. Each time point was separated by 6 months and over 24 months in total. The trajectories included a ‘low class’ which showed low levels of psychotic experiences reporting across various time points, an ‘increasing class’ which was considered to be a low level of psychotic experiences but one that increased over time, and an ‘elevated class’ which was characterized by initial elevated psychotic experiences but one that had decreased from time 3 to time 5. Using this model, Mackie et al. (2013) found that individuals who had experienced bullying 1-2 times per month were 2.37 times [95% CI 1.25–4.52] more likely to report ‘elevated’ psychotic experiences and 1.67 times (95% CI 0.97–2.86) more likely to report ‘increasing’ psychotic experiences. They also found that those who experienced bullying greater than 3 times per month were 3.43 times (95% CI 1.82–6.46) more likely to report ‘increasing’ psychotic experiences. In addition to bullying, it was further reported that cannabis use prior to age 14 impacted both ‘elevated’ and ‘increasing’ psychotic symptoms.

According to Mackie et al., adolescents who used cannabis before 14 years were 2.54 (95% CI 1.22–5.23) times likely to experience ‘elevated’ psychotic experiences and 2.16 (95% CI 1.20–3.90) times likely to experience ‘increasing’ psychotic experiences.
Furthermore, Mackie et al. found that there seemed to be a dose response relationship between the number of times a person used cannabis and psychotic outcomes. For example, they found that those who reported cannabis use only once were 1.90 times (95% CI 1.00–3.73) more likely to report ‘increasing’ psychotic experiences, and adolescents who reported cannabis use two or more occasions were 2.33 times (95% CI 1.25–3.96) more likely to report ‘elevated’ psychotic experiences. Compared with those who did not experience bullying or cannabis use, adolescents who experienced only one of the two risk factors (bullying or cannabis use) were 1.79 times (95% CI 1.00–3.22) likely to report ‘increasing’ psychotic experiences, and those who experienced both risk factors concurrently were 2.92 times (95% CI 1.45–5.78) to experience ‘elevated’ and 2.09 (95% CI 1.20–3.58) times as likely to experience ‘increasing’ psychotic experiences (Mackie et al., 2013). Because previous research has primarily focused on an association between environment and future psychotic experiences at only one point in time, this study provides evidence to show how psychotic symptoms may change over time when exposed to these two risk factors.

4.2 Report of Study Quality

While findings of the 16 studies composing this SR, provide converging evidence of the risk factors that are associated with adolescent cannabis use and subsequent symptoms of schizophrenia or long term psychosis, it is necessary to evaluate the methodological quality of these studies prior to drawing any definitive conclusions. In this section I provide an appraisal of the reporting and the methodological quality of these studies within their four respective table groupings by making use of the STROBE checklist (please see Appendix A). I start by presenting a summary of the methodological strengths of the 16 studies followed by
limitations. This will highlight the quality of these studies and elucidate some of the gaps in the research.

4.2.1 Table 1: Cannabis use in adolescence as a risk factor for psychotic illness.

As per the STROBE checklist, it appeared that the overall quality of the seven studies (Andreasson et al., 1987; Arsenault et al., 2002; Ferdinand et al., 2005; Henquet et al., 2004; Manrique-Garcia et al., 2011; Stephanis et al., 2013; Zammit et al., 2002) composing this table was good.

4.2.1.1 Strengths.

All of the studies clearly stated their study designs in the title and or abstract, and the abstracts all explained what was done and what was found. The exception was the study by Stephanis et al. (2013), but these authors did provide sufficient details in the abstract that allowed me to glean what the study was about and the design that was used. All seven studies had large sized samples. Typically a large sample size strengthens external validity, making results more generalizable amongst the respective population. I comment on the potential limitation of large sample size in a later section. Three of the studies (Ferdinand et al., 2005; Henquet et al., 2004; Stephanis et al., 2013) also made use of random selection which is one of the best ways to achieve unbiased results. This is because study subjects are drawn randomly from a large database, essentially giving everyone the same opportunity to be chosen (Polit & Beck, 2012). This sampling method also increases confidence in the external validity of the study due to the representativeness of that sample (Polit & Beck, 2012).

Most of the studies within this group provided a clear explanation of the variables that were examined as well as how they were analysed. However, as noted, the studies varied
with respect to what was identified as the main study outcome. For example, some studies specifically identified schizophrenia as the primary study outcome variable, whereas others considered a broader outcome such as psychotic symptoms or they focused on diagnosis of schizophreniform disorder. Some also examined more than one outcome variable (i.e., schizophrenia and other psychosis, schizophrenia accompanied by depression, and other non-affective psychoses including psychotic outcomes such as paranoia, hallucinations, etc.).

While methodologically speaking it would be more accurate to compare studies on a single outcome, the varied diagnosis is more reflective of clinical practice which is important. A further strength is that all seven studies controlled for known confounders by virtue of their study design, or through statistical analysis. As well all made use of valid and reliable tools. These strategies help reduce potential bias by ruling out rival explanations for various cause and effect relationships and the use of validated tools helps generate valid study findings. In addition, some studies (whether intentional or not) addressed bias through using a sample that was homogenous (male only samples).

All seven studies provided detailed reports related to data collection procedures and their approach to data analysis. This helps optimize internal validity through the use of standardized study data collection, inter-rater reliability procedures and measurement approaches. In the Zammit et al. (2002) study it was reported that there would be a decreased likelihood of false reports related to cannabis use, as cannabis is generally condoned in Netherlands. Additionally Andreasson et al. (1987) and Ferdinand et al. (2005) both reported on effect size (HRs and RRs) within their studies, allowing the reader to have a more accurate understanding of the strength of the relationship between the variables (Polit & Beck, 2012).
Each of the seven studies provided fairly comprehensive reports of their results however some tended to be more complete than others. For example, although all of the studies reported on the main findings some did not provide information about study participants. Five of the seven studies gave results that included both unadjusted and confounder adjusted estimates. Including both the unadjusted and adjusted results allows the reader to understand what was done statistically, but also allows for a comparison of the results and to see how much, and in what direction, the results had changed (Vandenbroucke et al., 2007). The major findings that were shared amongst all seven studies were that there is indeed a relationship between cannabis use during adolescence and the onset of psychotic symptoms or schizophrenia later in life. These results were compared with previous studies and seemed to support those findings from prior studies (Arsenault et al., 2002; Ferdinand et al., 2005; Henquet et al., 2004; Manrique-Garcia et al., 2011; Stephanis et al., 2003).

Most of the studies provided a discussion section in their report, where the discussion included a brief synopsis of key findings, explanations and comparisons of key findings from other studies, strengths and limitations, and summaries of the implications for practice (Vandenbroucke et al., 2007). And, all studies within this group provided acknowledgement to funding sources. The recognition of funding sources is important as it makes transparent any potential conflicts of interest and allows the reader to see if there are any associations between the source of funding and conclusions identified within the research articles (Vandenbroucke et al., 2007).

4.2.1.2 Limitations.

Despite the several strengths mentioned above, there were some limitations within this group as well. Three of the seven studies made use of convenience samples (Andreasson
et al., 1987; Manrique-Garcia et al., 2011; Zammit et al. 2002) and chose to use only male subjects (Andreasson et al., 1987; Manrique-Garcia et al., 2011; Zammit et al., 2002). Convenience sampling is a method that uses participants who are convenient (as the name implies) to access (Polit & Beck, 2012). This form of sampling is considered weak as it can limit generalizability (Polit & Beck, 2012). And although three studies (Andreasson et al., 1987; Manrique-Garcia et al., 2011; Zammit et al., 2002) had very large samples, it is important to recognize that extremely large samples can be at risk for introducing a type I error. Therefore, it is important to keep in mind that a large sample provides no guarantee of accuracy as it cannot correct for a faulty design (Polit & Beck, 2012). With the exception of Henquet et al. (2004), none of the remaining six studies reported having conducted an a priori power calculation to determine their required sample size. Longitudinal studies should consider their sample size a priori, and in doing so should also take into account potential attrition from the study in determining sample size. Again, it is quite possible that secondary studies, such as the one carried out by Arsenault et al. (2002), did not indicate the power analysis in their current report. However, because none of this information was indicated in the current report, it leaves the reader to conclude that it had not been done. Lastly, the three conscript studies (Andreasson et al., 1987; Manrique-Garcia et al., 2011; Zammit et al., 2002) included only male subjects. This is a shortcoming in that an all-male sample threatens the external validity of the study and negates understanding of females.

A final but important limitation was that only three studies provided adequate explanation of missing data or how they may have dealt with missing data. Of these three studies, Henquet et al. (2004) reported that they used sensitivity analysis to examine whether attrition in their sample may have biased findings, and to accomplish this, these researchers
performed “multiple imputation of missing values of cannabis use at baseline, predisposition for psychosis at baseline, and psychotic symptoms according to the CIDI at follow up” (Henquet et al., 2004). Manrique-Garcia et al. (2011) indicated that 16.3% of subjects had missing information in the variables included in the model, and that 6.8% did not respond to the question on drug use. Therefore these investigators used only 41,943 out of the original 50,087 subjects for their final analysis. Ferdinand et al. (2005) indicated that they corrected for drop outs and other forms of attrition, however they did not specifically discuss how this missing data was dealt with. The remaining four studies did not discuss missing data or attrition.

According to the STROBE checklist statistical techniques assume (or require) complete data, therefore incomplete or missing data may provide misleading results (Vandenbrouke et al., 2007). This issue is important because participants are free to withdraw from a study for any reasons and is especially important for longitudinal studies because these types of studies are highly prone to attrition and to loss in follow-up. The loss to follow-up may hamper the validity of that study (introducing attrition bias), particularly if it occurs selectively in exposed individuals, or in individuals who are at high risk of developing the disease (Vandenbrouke et al., 2007). According to Vandenbrouke and colleagues, reporting of missing or incomplete data should occur for each variable of interest (exposures, outcomes, confounders) in each step of the analysis. Additionally, authors should provide reasons for why there are missing values and provide a report of how many individuals were excluded as a result of any drop outs (Vandenbrouke et al., 2007).

Various forms of bias were present within each of the studies as well. For example, the retrospective nature of the data collection methods in three of the studies (Ferdinand et
al., 2005; Stephanis et al., 2013; Zammit et al., 2002) had the potential to introduce recall bias. Recall bias is the discrepancy between what actually occurred and what the subject remembers, and sometimes information is not always complete or accurate when trying to recall an event from the past (Polit & Beck, 2012). Additionally, where Henquet et al. (2004) used self-reports of psychotic experiences, this too may have presented recall or reporting biases into their study, especially if the individual was sick when the past event occurred, or when the interview took place. Furthermore, Henquet and colleagues obtained information from study subjects initially using self-reports, but then the investigators later used the CIDI to identify psychotic experiences at follow up. This switching of methods may have challenged the reliability between subject reports of symptomology versus results from a formal diagnostic tool.

As mentioned, some of the studies provided incomplete reporting of the study (i.e., type of study design) or how the study was carried out. Arsenault et al., (2002), for example, neglected to report drug use between the ages of 11-15 years in their sample, and also failed to discuss limitations, and another study (Andreasson et al., 1987) gave only limited information about the duration of cannabis use which made it difficult to determine whether or not cannabis use was considered ‘heavy’ use. Under-reporting limits confidence that findings are based on rigorous study methods.

Lastly, although four of the studies (Andreasson et al., 1987; Ferdinand et al., 2005; Henquet et al., 2004; Zammit et al., 2002) reported having adjusted for confounders in the statistical analysis, they did not explicitly state the statistics that were used. The STROBE checklist advises that statistical methods be described with enough detail to enable a
knowledgeable reader with access to the original data to verify the reported results (Vandenbroucke et al., 2007).

In sum, although there were several limitations amongst this group of studies, the strength of the evidence as a whole was good and it provided a valuable contribution to the body of knowledge on this topic.

4.2.2 Table 2: Impact of adolescent cannabis use on neurodevelopment.

As with the previous group of studies, the overall quality of this group of five studies (Cohen et al., 2012; James et al., 2011; Kumra et al., 2009; Peters et al., 2009; Solowij et al., 2011) was good.

4.2.2.1 Strengths.

All provided sufficient details about the setting (i.e., location, dates, recruitment strategy, exposure, follow-up, and data collection) and the participants (i.e., eligibility criteria, sources and methods of selection, and methods of follow-up), as well as the locations for each study. The introduction, which included the background and rationale, was also comprehensive amongst the studies within this group and a clear explanation of the various objectives and or hypotheses were also provided.

The four studies that made use of a case-control design (Cohen et al., 2012; James et al., 2011; Peters et al., 2009; Solowij et al., 2011) provided information about participants and rationale for their choice of cases and selection of controls. In addition they gave clear descriptions of their matching criteria and the number of controls that was used per case. According to the STROBE tool (Vandenbroucke et al., 2007), the choice of cases and controls is necessary for being able to interpret results, and the method that is used for selecting the controls also has implications for validity. There may be various methods used to obtain
controls, therefore it is important that controls that are chosen reflect the population for which the cases came from (Vandenbrouke et al. 2007). Kumra et al. (2012) was the only study within this group that used a cross-sectional design, thus there were no matched controls.

Within this group of five studies all variables, independent and dependent, were observed and measured using valid and reliable instruments. Three studies (James et al., 2011; Peters et al., 2009; Solowij et al., 2011) that made use of the DSM-IV to identify patients who had a psychiatric diagnosis of schizophrenia also had trained professionals (psychiatrists or other trained psychology assistant) conduct the interviews. As well, the outcomes were observed through MRI technology which is considered to be a highly reliable and valid method for obtaining images of brain structure.

The four case-control studies (Cohen et al., 2012; Kumra et al., 2012; Peters et al., 2009) minimized bias through study design (i.e., by matching subjects on age, gender, handedness, etc.) and statistically. The subjects were divided into healthy controls and those who had a psychiatric diagnosis of schizophrenia, as well as those who used cannabis and those who did not. Having these four separate groups minimized bias by limiting the potential effects from confounders. Kumra et al., unlike the other four studies, also used ANCOVA to control for age, sex and reading score for adolescents with schizophrenia compared with healthy control subjects and nonpsychotic adolescents. This is as would be expected considering they did not use matched controls within the design of the study (Kumra et al., 2012).

Since the purpose of all studies within this group was to identify whether or not there was an observed relationship, or to predict whether or not there might be a relationship
between cannabis use and neuroanatomical changes in the brain, the statistical analyses that were used seem to be appropriate for these studies.

The results from these studies showed that there is a relationship between cannabis use and structural changes in the brain. All studies presented clear and comprehensive results and visual depictions of the results were further shown in tables for ease of comprehension. Key findings were presented and were consistent with respect to the study aims. Peters et al. (2009), although they too were able to identify structural changes in the brain of subjects who used cannabis, their results were contradictory to the other studies in that there appeared to be increased white matter instead of decreased brain matter. Despite observing changes, these authors commented that their findings were unexpected and that they were in contrast to previous research on the same topic. However, the authors did indicate that there were some methodological limitations of their study, thus it is possible that these findings are inconclusive as the results may not have been related solely to the specific use of cannabis, but may have been an effect of other hard drug use as well. All studies, with the exception of Peter et al. (2009), provided information about their funding sources, making it transparent as to whether or not there would be any potential conflicts of interest.

4.2.2.2 Limitations.

Despite the above mentioned strengths amongst this group of studies, there were some limitations. For example, sample sizes amongst all studies appeared to be quite small, thus limiting the interpretation of the results as well as the generalizability of those results as well. If a study is not large enough, then the confidence that one has in the results are less, particularly if the aim is to distinguish a small association from no association.
(Vandenbrouke et al. 2007). Furthermore, none of the studies discussed how sample size was arrived at, nor did they perform a power analysis. Without a power analysis, it is difficult to see whether or not the sample sizes of these studies were sufficient enough to answer the research question or detect important effects or associations (Zodpey, 2004). Small sized study groups also may introduce type II error (failure to detect a targeted outcome when in fact the outcome may have occurred). Two studies used only right-handed male subjects (Peters et al., 2009; Solowij et al., 2011). Although limiting sample by gender and handedness may increase homogeneity and control for the potential confounding of gender and handedness, this approach posed a threat to the external validity and it negates understanding for females or those who may be left handed. Additionally, the samples were all based on convenience sampling which also may have further limited the generalizability of the findings.

Another major shortcoming within this group of studies had to do with a lack of reporting in some areas. For example, amongst the entire group, the study designs were not clearly stated in the title and/or abstract, which made it difficult to immediately see what type of study was conducted. Furthermore, the designs of these studies were not referred to explicitly within the text either, thus the reader had to infer the study type. Also none of the four studies reported on missing data and no sensitivity analyses were conducted. The lack of reporting on missing data reduces transparency and because missing data may bias or affect generalizability of results; authors should have indicated the amount of missing data for exposures, potential confounders, and other important characteristics of patients. As well, all of the studies failed to report on both unadjusted estimates and confounder-adjusted estimates, making it difficult to see which confounders were adjusted for and why.
Lastly, there was the limitation of potential recall bias within some of the studies, which related to information that was obtained retrospectively (i.e., cannabis use patterns). Furthermore, both Cohen et al. (2012) and Kumra et al. (2012) indicated that a majority of early onset schizophrenia subjects in their study had been treated with antipsychotic medication at the time of the MRI examination. As mentioned earlier, information inaccuracy can arise because individuals are ill or they may not remember events accurately.

The overall evidence amongst this group of studies provided novel preliminary data that showed that there are observable changes in the brain in individuals with schizophrenia and in those who consume cannabis. However because of the aforementioned limitations and preliminary nature of the findings, additional larger studies on this topic are needed to both confirm these findings but also to identify the pathways for which these changes occur.

4.2.3 Table 3: How Genetics/epigenetics relate to the onset of psychosis in adolescents who use cannabis.

Group three, as explained previously, consists of only one study (Estrada et al., 2011). The overall quality of this study was good; however the evidence may have been strengthened if other studies were used as well for comparison.

4.2.3.1 Strengths.

Some of the strengths of the Estrada et al. (2011) study were that the background and rationale and study purpose were clear and well explained. Because this was a case-control study individuals with psychiatric, but non-psychotic, disorders were used as controls, thus confounders were controlled for by means of the inclusion and exclusion criteria (study design). Additionally, the independent and dependent variables were measured and identified using valid and reliable measurement and assessment tools such as blood tests and
buccal swabs to identify DNA, and, as with previous studies, the DSM (IV) was used to
determine diagnosis.

The statistical analyses consisted of using simple linear regression, t-tests and chi-
square, which were all appropriate for addressing study aims. They were also appropriate for
the small sized study sample. For example, t-tests were used to compare the means of
continuous variables between two groups and chi-squared tests were used to analyse the
distribution of qualitative variables between groups. Linear regression analysis was
conducted as to see what the effect of both gender and age at first consumption had on age of
onset of psychiatric symptoms and also aimed to test the effect of the interaction between age
at first cannabis use and COMT Val158Met genotype on the age of onset of psychiatric
symptoms. Potential confounders were dealt with by means of the study design, using
specific exclusion criteria for eligibility amongst subjects at the beginning of the study.

The results and the discussion sections of this paper were also well explained and
thorough. Because confounders were controlled for through the inclusion and exclusion
criteria, there was no requirement of the authors to report on adjusted versus the unadjusted
results for confounders in this section. All acknowledgements towards sources of funding
and the role of the funders for the present study were included at the end of the report, thus
making it transparent as to whether or not there is a potential conflict of interest.

4.2.3.2 Limitations.

As with the previous two table study groupings (Table 1: Cannabis use in
adolescence as a risk factor for psychotic illness; Table 2: Impact of adolescent cannabis use
on neurodevelopment), there were several limitations related to adequate reporting. For
example, the title and abstract did not make clear the study design. Additionally, although
the objective and hypotheses were clearly articulated, the methods that were used to carry out this study were lacking and key elements of the study design were not presented early in the paper. Information about the setting was also incomplete. The investigators explained, for example, that subjects were recruited and that data on subjects were obtained from admissions and hospital records, however the report failed to provide information about the hospital location and any relevant dates for which data were collected. The study indicated that the psychiatric inpatients were consecutively recruited and interviewed by psychiatrists and psychologists. A random sampling approach would have been a stronger method for which to reduce the risk of sampling bias. But it is important to mention that compared to convenience sampling, consecutive sampling is a stronger sampling approach for reducing bias because it allows everyone an equal chance to participate in a study during the defined time block of recruitment. Another limitation is that no power calculation was conducted. The sample size may have potentially been too small to detect important findings or significance, or the possibility of a type II error may have occurred.

As with the previous study tables this report also failed to indicate whether or not there were any missing data, leading the reader to believe that there was none, or that there were missing data but that it was not handled appropriately. Furthermore, this study also may have been subject to recall bias. Recall bias may have stemmed from subject accounts of when they first used cannabis and how often, as well as the amount of THC used or type of cannabis that was used by individuals. This is important considering the age at first exposure to cannabis was one of the main independent variables. This systematic error could potentially impact the results of the study, leading to inaccurate conclusions. Lastly, the
authors did not report any limitations of their study, which may have either represented incomplete reporting, or they simply did not think that there were any limitations.

Despite the aforementioned limitations, this study adds to the evidence that age at first cannabis use modifies the age at onset of both psychotic and non-psychotic disorders, and that the effects of cannabis may be related to neurodevelopment and maturity at the moment of first exposure. It further shows that early exposure to cannabis may be related to genetic background and that this connection may be related to the COMT gene (Estrada et al., 2011), where genetic predisposition is a mediating factor in this relationship.

4.2.4 Table 4: Childhood trauma as a risk factor for psychotic symptoms in adolescents who use cannabis.

As in the preceding three table groupings (Table 1: Cannabis use in adolescence as a risk factor for psychotic illness; Table 2: Impact of adolescent cannabis use on neurodevelopment; Table 3: How genetics/epigenetics relate to the onset of psychosis in adolescents who use cannabis), this group of three studies (Harley et al., 2010; Houston et al., 2008; Mackie et al., 2013) presented with several strengths and limitations.

4.2.4.1 Strengths.

Each of the studies provided detailed abstracts, indicating what was done and what was found, the introductions were thorough, with the backgrounds and rationale for each study clearly stated, and the objectives and or hypothesis were provided. Both Harley et al. (2010) and Mackie et al. (2013) also provided good descriptions of the location, dates, recruitment and data collection as well as the eligibility criteria, methods of selection, and methods of follow-up for their participants, and the sample size of two of the three studies (Houston et al., 2008; Mackie et al., 2013) were relatively large. Houston et al. (2008) used
a national representation of subjects (from the United States of America), which made the findings of their study fairly generalizable amongst that population. However, it is important to keep in mind that a shortcoming of any study that uses a large sample size is that there is a potential for type I error, otherwise known as a false positive.

All three studies showed strength in reporting on the variables under study, with all three studies clearly explaining how the variables were analysed, the statistical methods that were used (including methods to address confounders), and the methods to examine subgroups and their interactions. These studies used both valid and reliable assessment and or diagnostic tools. Confounders were controlled for, where two out of three studies (Houston et al., 2008; Mackie et al., 2013) indicated that they had adjusted for confounders through statistical analysis while the remainder (Harley et al., 2010) controlled for confounders by virtue of the study design, and used a matched comparison group.

The statistical analyses that were used in the three studies were appropriate for the aims of the studies and the questions that investigators sought to obtain. Additionally, two of the three studies (Harley et al., 2010; Houston et al., 2008) also reported effect sizes (ORs). As mentioned earlier, the reporting of effect size is valuable in that it allows the reader to understand the magnitude of the strength of the relationship between variables.

Bias in all three studies was minimized by controlling for confounders. It was also minimized, as described in Harley et al. (2010), by obtaining intra-rater reliability k=.90 during interviews, through using random stratified sampling methods (Harley et al., 2010), and through having a comparison group that was matched for gender and school (Harley et al., 2010).
The results in this group of studies were presented well, with all three giving both the unadjusted estimates and confounders, making it clear which confounders were adjusted for and why. Two of the three studies reported on other analyses that were done such as analyses of subgroups, interactions, etc. (Houston et al., 2008; Mackie et al., 2013). The discussion section was also comprehensive in all three, providing key results with reference to study objectives. The studies also discussed limitations and, except for Houston et al., they made mention of any funding sources.

4.2.4.2 Limitations.

As with the previous three tables the studies within this table possessed various limitations. For example, only one mentioned the study design that was used (Mackie et al., 2013), making it necessary for the reader to deduce the type of design from the information in the report. The Mackie et al. study also indicated the key elements of their study early in the paper, allowing the reader to immediately understand what the study would be about without having to read through the entire report. Of the three studies, the study by Houston et al. (2008) gave only brief, incomplete information about the study setting and the participants within the study. And, although all three studies provided some information about the characteristics of study participants (i.e., demographic, clinical, social) only one reported on the number of subjects during various stages of study (Mackie et al., 2013).

In two of the three the studies, samples sizes seemed fairly large (Houston et al., 2008; Mackie et al., 2013), however none of the three studies indicated how their sample size was arrived at and there was no power calculations performed. Neglecting to perform a power analysis is a significant shortcoming for the reasons previously mentioned. Additionally, although Mackie et al. appeared to have a relatively large sample size
(N=1098) these investigators chose to use a convenience sample rather than a random sample. Again, convenience sampling decreases generalizability of the findings, thus threatening the external validity of this study.

None of the studies within this group discussed whether or not there were missing data, and thus did not explain how missing data were addressed. In addition, all three studies neglected to provide reasons for non-participation at each stage, and additionally, the studies lacked in providing information about the number of participants with missing data, with only one of three studies provided information related to the follow-up time (Mackie et al., 2013). This was a significant shortcoming as explained earlier, missing data that occurs due to loss of follow up can hamper the credibility of a study, particularly when the missing data has not been handled appropriately. A sensitivity analysis would have been beneficial to account for any drop out or deaths, but also with studies for which there may be selection bias (Vandenbrouke et al., 2007).

Lastly, there were several limitations within each of the studies that were acknowledged by the authors themselves. For example, in Mackie et al. (2013) psychotic experiences were based on self-reports by subjects and were not independently confirmed, in Harley et al. (2010) and Houston et al. (2008) there may have been under-reporting on rates of cannabis use, sexual abuse, etc., and in Harley et al. recall bias with respect to childhood trauma may have provided inaccurate or incomplete data.

However, despite the various shortcomings, these three studies were of value to this SR in that they provided evidence to show how risk factors such as childhood trauma can add to the risk for developing a psychotic disorder in adolescents who consume cannabis. Findings help to explain how trauma can mediate the effects of cannabis use thus increasing
the strength of the proposed trauma-psychosis relationship (Houston et al., 2008), how childhood trauma can act as a potential effect modifier (Harley et al., 2010), and how the risk of developing psychosis is elevated in adolescents who experience bullying by peers and who use cannabis (Mackie et al., 2013).

In sum, the methodological assessment shows several strengths amongst the 16 studies contained in this SR that support study findings and conclusions. No study is ever free of methodological shortcomings and each of these 16 studies is methodically complex. However, to strengthen the quality of evidence, authors of future studies in the four areas should provide more detailed information about how sample sizes were arrived at or how missing data was accounted for. It is also important to conduct an a priori power analysis to calculate study sample size and to employ measures of effect size as appropriate. Furthermore, inclusion of both male and female subjects is recommended to strengthen the external validity of all studies. By addressing these issues, a greater confidence in the results of these studies would be gained.
Chapter 5: Discussion and Conclusion

This section provides a summary of the main findings and contributions of this SR comparing the findings to a similar published SR. In this discussion I also provide an overview of strengths and limitations of the studies composing this SR, but also for the SR itself, discussing ways in which it could be improved. Lastly, I discuss the implications of this research and conclude by providing my recommendations for further nursing education, research and practice.

In this SR I used a neurodevelopmental theoretical framework to guide my selection of studies. This framework helped me to identify several of the risk factors, individual and environmental, associated with the development of schizophrenia and other psychoses during adolescence. The framework illustrates the importance of timing, where the stage of brain development during adolescence is one of the key risk factors in this equation. The framework helps to understand how this critical period can be influenced by various environmental risk factors and why the teen years pose a time of great vulnerability. Furthermore, as no single cause has been attributed to early development of schizophrenia, this framework also helped to gain a better understanding as to why not all individuals who consume cannabis end up developing schizophrenia and other psychotic disorders.

Taken together, the main findings of the 16 studies within this SR show that there is some convincing evidence to support that there is a range of factors that contribute to the relationship between cannabis use during adolescence and early onset of schizophrenia or other long term psychotic symptoms. When considered together, these conclusions are based on more complete and compelling foundation of evidence, than when the findings of the individual groupings are considered in isolation of each other. For example, findings of the
first seven studies from Table 1, which examined cannabis use in adolescence as a risk factor for psychotic illness, provided evidence that cannabis use during adolescence is strongly associated with a subsequent onset of psychotic symptoms or schizophrenia (Andreasson et al., 1987; Arseneault et al., 2002; Ferdinand et al., 2005; Henquet et al., 2004; Manrique-Garcia et al., 2011; Stephanis et al., 2013; Zammit et al., 2002), particularly in frequent or heavy use. The five studies in Table 2 that examined the impact of cannabis on neurodevelopment further support this evidence, show that adolescents who consume cannabis early, frequently, and heavily, have objective MRI-based neurodevelopmental changes that resemble changes that occur in the brains of individuals who have schizophrenia (Cohen et al., 2012; James et al., 2011; Kumra et al., 2012; Peters et al., 2009; Solowij et al., 2011).

The study in the third table which examined genetics/epigenetics (Estrada et al., 2011) provided evidence to support that cannabis alone, even during adolescence, may not be the sole contributing factor to the onset of long term psychosis, but that it may not be exclusive of genetic predisposition. Genetics may in fact, be one of the key underlying factors responsible for influencing the emergence of psychotic disorders, and where genotype may also modulate the association between cannabis use and age at onset of psychotic disorders during the critical period of adolescent brain development. And lastly, the evidence from the three studies in table 4 which examined childhood trauma as a risk factor suggests that early adverse experiences may play a role in the relationship between cannabis use and early onset schizophrenia or psychosis. They show that cannabis may act as a mediator to increase the strength of the proposed trauma-psychosis relationship (Houston et al., 2008), that childhood trauma may function as a potential modifier effect (Harley et al.,
2010), or that the effect of bullying by peers and cannabis use is associated with increased psychotic experiences over time (Mackie et al., 2013). This evidence adds to the complexity of the relationship and the interactions between variables (adolescent cannabis use and the onset of psychotic disorders). It shows that if an association between these factors is present that there may be other factors as well that could contribute to the same outcome.

Over the past 25 years, studies within this area of research have continued to evolve and grow in number. Andreasson et al. (1987) presented one of the first seminal studies that looked at the relationship between cannabis use and schizophrenia, but since that time, the number of published studies that have examined the association between cannabis and its impact on mental health has grown. However, apart from this SR, there has only been one other SR conducted that has summarized the evidence on cannabis as a risk factor for psychosis in adolescence and early adulthood (Semple et al., 2005). The SR by Semple et al. (2005) consisted of 11 case-control and cohort studies. The SR by Semple et al. (2005) also differed from the SR that I have conducted, is that the SR by Semple et al. examined cannabis as an independent risk factor for schizophrenia, psychosis, and psychotic symptoms but it did not include studies that examined a wider range of additional risk factors (i.e., neurodevelopment, genetics, trauma in childhood, etc.). The Semple et al. SR also looked at studies where cannabis use preceded the onset of psychotic illnesses however it did not specifically focus on the adolescent population. Furthermore, Semple et al. were able to conduct a meta-analysis of the findings (ORs) for 7 out of the 11 case control and cohort studies these authors obtained for their SR. On the basis of their SR, Semple et al reported that there is strong evidence to conclude that cannabis is a risk factor to the development of schizophrenia or a schizophrenia-like psychotic illness during adolescence and early
adulthood, with the ORs being approximately three-fold (Semple et al., 2005). Although I did not conduct a meta-analysis, the overall conclusion made by Semple et al. is consistent with my overall conclusion. Also similar to the findings from my SR, Semple et al. suggest that cannabis use during adolescence or early adult life may be one of a number of environmental stressors that interact with genetic factors to predispose an individual to later psychotic illness. The authors’ further report that cannabis use is neither necessary nor sufficient to cause psychotic illness but that it may simply be a risk factor that impacts vulnerability and timing of the onset of the psychotic illness.

In agreement with Semple et al. (2005), the findings of this SR do not permit one to conclude that cannabis use is a cause of schizophrenia or other psychotic outcomes. However, my findings do provide some evidence that there is a relationship between these factors, and that the relationship may be stronger when other potential risk factors exist concurrently. On the basis of this SR, it can be further concluded that adolescent youth who have many, if not all, of the risk factors that were identified in the studies I reviewed (i.e., early and heavy use of cannabis, genetic predisposition and childhood trauma), would be those most likely to develop schizophrenia. Basically, each added risk factor heightens the risk for psychotic illness, cumulating to create what I like to think of as a perfect storm metaphorically speaking. However, while my findings suggest a strong association between these variables and that some function as underlying factors while others act as mediators, the exact pathways of association between cannabis use during adolescence and the onset of schizophrenia or other psychotic illness is still not clear. Findings from this SR may serve as the basis for future studies to help clarify these pathways of association. The findings will also help demonstrate the robustness of the findings from the reviewed studies which might
allow for early detection of those at risk, and for adequate intervention strategies to be developed.

The studies that were reviewed in this SR presented with many methodological strengths, thus giving much confidence in their findings. I found that of the 16 studies that I reviewed, almost half made use of large sized study samples (Andreasson et al., 1987; Arsenault et al., 2002; Ferdinand et al., 2005; Henquet et al., 2004; Houston et al., 2008; Mackie et al., 2013; Manrique-Garcia et al., 2011; Stephanis et al., 2013; Zammit et al., 2002), and that all made use of validated study instruments and all controlled for a variety of potential confounders. Furthermore, several employed matching within their study design to limit variability between subjects (Cohen et al., 2012; James et al., 2011; Peters et al., 2009; Solowij et al., 2011) and some reported on their measure of effect size (Andreasson et al., 1987; Ferdinand et al., 2005; Harley et al., 2010; Houston et al., 2008).

However, many of the 16 studies could benefit from replication. On the basis of the critical appraisal, future studies should aim to strengthen their reporting on missing data and how missing data were handled, they should include a priori power calculations when determining sample sizes for their studies, and they should consider including both male and female subjects to strengthen the external validity of their findings. Under-reporting of missing data is a significant shortcoming, especially for longitudinal studies where we know that by virtue of the study design that there is a high, almost definitive likelihood that data will be missing. Subjects drop out, die, or simply do not follow up with investigators over long periods. Currently, several statistical/analytic programs, procedures and guidelines exist and are recommended for handling/reporting of missing data for longitudinal studies such as multiple imputation depending on the reason data is missing (i.e. missing completely at
random (MCAR), missing at random (MAR) and missing not at random (MNAR). Croy and Novins (2005) provide discussion on the use of these methods for psychiatric and development research.

A power analysis is very important, again particularly in longitudinal studies where attrition can be high (Hedeker, Gibbons & Waternaux, 1999). Although several studies appeared to have very large sample sizes, the results from these studies do not necessarily infer causation, nor do they necessarily reflect the reality of the situation. As mentioned previously in this thesis, there is the potential for extremely large sample sizes to present a type I error (aka. false positive). It is well known that not only male, but females as well, consume cannabis during adolescence. And although women do tend to develop psychotic disorders later than males (Canadian Mental Health Association, 2014; Hafner et al., 1998; Lewine, 1980; Loranger, 1984), current evidence on risk based on male samples alone can only be regarded as inconclusive.

5.1 SR Limitations

This SR also has some limitations. All in all, the studies used in this SR provided some good evidence to show the factors involved in the development of psychotic symptoms in adolescents who consume cannabis. The selection of studies for the SR was based on the use of intra-rater reliability. One of the ways in which this SR may have been strengthened would have been to use inter-rater reliability testing for both selection and rating of the studies. The inter-rater reliability procedure calculates agreement in rating between two raters and if the calculation is based on Cohen’s kappa it takes into consideration systematic error (Kottner et al., 2011). While I also calculated an intra-rater reliability making use of Cohen’s kappa to ensure that my selection and ratings of studies were consistent over time,
the use of inter-rater reliability employing two independent raters (myself and my supervisor) might have been a more robust approach. This SR took into consideration a number of potential risk factors. But, it is possible that there are additional risk factors that I did not examine and that were mentioned in Chapter 1 of this SR (i.e., perinatal exposure to influenza and teratogens, obstetric complications, season, geography of birth, urbanisation, immigration, famine and other stresses, attachment issues, neglect, socioeconomic poverty, etc.) (Leask, 2004; Read, Bentall & Fosse, 2009). Also, although 16 studies were identified for this SR, the search ended on July 31, 2014. Future research should continue to add studies that meet these search and study quality criteria. Conducting a larger, more comprehensive SR using this same researchable (PICO) question may perhaps be a recommendation for future SR’s of this kind.

Some may question why I did not make use of a scoring tool for rating methodological quality. I do not consider this issue to be a limitation or shortcoming of this study. There are scoring tools available, such as The Newcastle-Ottawa Scale (NOS) (Wells et al., 2014), for example. However the reason I chose not to use a scoring tool was because a main aim of this SR was to provide an in-depth narrative summary of the studies and their methodological strengths and limitation. Traditionally a scoring tool would only provide a numerical summary score of quality. Yet, the resultant summary score generated cannot pinpoint methodological strengths, shortcomings and gaps requiring improvement. In this study I found that the STROBE checklist in combination with the knowledge gained in my research courses allowed me to critically appraise each study in a systematic and thorough manner.
5.2 Implications for Practice

As explained above, adolescence is a normative critical period of remarkable changes in neurodevelopment. During this critical period in development, the heavy consumption of cannabis can introduce an avoidable environmental risk to the onset of schizophrenia and other psychotic disorders. Although not every adolescent who consumes cannabis will end up developing a psychotic disorder, the findings from this SR clearly show that accompanied by other significant risk factors, the use of cannabis can significantly increase the risk for development of these disorders. There are several implications of this SR.

There has been much information about the benefits of cannabis use over the recent years, especially with respect to its medicinal use. Although there is likely some beneficial properties of cannabis (which will not be debated in this discussion), it is important to consider the risks, particularly amongst those who are most vulnerable, so that we do not put the cart before the horse, so to speak. Given the diverse political views on whether or not recreational cannabis use should be legalized, the direction and development of public policies will depend on what political party is in power. In the US, four states will have legalized the recreational use of cannabis by July, 2015 (Norml, 2015). In Canada various factions are debating whether or not to legalize cannabis. Basically, public policy needs to be rooted in and guided by current and sound evidence. The evidence presented in this SR is not intended to support nor oppose legalization of recreational cannabis use. It is intended, however, to share the most current evidence on this subject, so that decisions may be well thought out prior to changing current legislation.

The synthesis of the evidence from this SR can be used to develop education strategies targeted to members of the general public (adolescents, parents and other
caregivers), those who work within the healthcare field (nurses, doctors and other health care clinicians), those who work in school system, and those within the government. It is important that such key stakeholder individuals and groups be provided a summary of the current evidence as it will help increase understanding and heighten awareness of comorbidity during adolescence and of the potential harms of cannabis use and the significant risk it poses during this vulnerable stage of neurodevelopment. Strategies for sharing this information should aim to inform key stakeholders of these potential risks and to debunk any myths or misunderstandings that people may have with respect to cannabis use, such as the idea that it is solely a benign, natural substance.

Specific areas of nursing practice which will benefit the most from key findings of this SR are those areas that deal with either mental health and addictions or children and youth. Nurses are in key positions to provide education, but also to screen for drug use in the clinical area, to develop programs which focus on prevention strategies, and to work on developing this research further. Nurses are also responsible for sharing knowledge amongst not just clients, but colleagues, students and others as well (College of Registered Nurses of British Columbia, 2014). It behooves the nurse who is working with children or adolescents, or in the area of mental health and addictions, to not only increase their own knowledge on this subject but to share it with their colleagues, clients and the public as to provide an awareness of the risk’s associated with cannabis use amongst this vulnerable adolescent population. Therefore dissemination of this information is paramount.

Ways in which main findings of this SR can be shared are through various knowledge translation (KT) and dissemination strategies. KT requires planning, producing, disseminating, and applying existing or new knowledge to enhance the health of Canadians
Potential KT avenues for this SR are: publication of the SR in peer-reviewed journals, educational outreach (i.e. presentations and engagement with stakeholders face to face), materials (i.e. paper or web-based documents), and social media (i.e. Facebook, Twitter, Blog sites, school websites and forums, etc.). Other future strategies might include presenting these findings to various key stakeholders such as youth, parents, and other health care professionals within various health care and educational settings. This information could be shared at facilities such as BC Children’s Hospital, the Ministry of Children and Families, or in K-12 schools for example.

As nurses and researchers it is expected that we educate the public of these potential risks so that individuals are able to make informed decisions based on the best available evidence. It is important that youth are aware of the potential consequences of cannabis consumption on neurodevelopment so that they may make well informed decisions about whether or not to engage in cannabis use, and so that they may share this information amongst their peers. It is equally necessary that parents, health care professionals and those who work in the schools, be knowledgeable about potential risk factors and consequences so that they can be alert to the signs that an individual might be using cannabis, or work on ways for informing adolescents about them. And because there continues to remain much debate in the political arena about whether or not to legalize (or just decriminalize) cannabis use in Canada, whatever the decided outcome, this decision should also be based on the best available evidence as well. This SR provides such evidence, and it also provides a base for which to explore this topic further.

Future SR’s of this kind could benefit from examining a broader range of risk factors. Improvements in the methodology of future studies may also permit future meta-analysis to
gain a more clear understanding of the state of the science and future directions for prevention and treatment. It is only through greater knowledge of the effects of cannabis on the developing adolescent that known risks can be reduced or ameliorated all together. And perhaps with a greater understanding of relevant factors and their complex pathways of association, a greater understanding of psychotic illnesses such as schizophrenia will also emerge.

In conclusion, this SR provided a synthesis of findings and a narrative appraisal of the methodologic strengths and limitations of 16 studies relevant to addressing my PICO question. Findings of this SR show there is significant evidence to support the conclusion that a number of factors are strongly associated with onset of schizophrenia and other psychotic illnesses in adolescents who consume cannabis. Researcher can make use of findings of this SR to identify areas for improvement to strengthen future examination of neurodevelopment impacts and to clarify the complex pathways underlying early onset schizophrenia which has profound implications for quality of life. The findings also serve as a credible basis for development of dissemination strategies to inform key stakeholders including youth, family and policy makers on the findings of association. Although the findings and current state of science are inclusive of causality, the evidence of strong association warrant future improvements in study methodology and informed decision making regarding heavy cannabis use during adolescence (which is avoidable) and its association with early onset schizophrenia, particularly for sub-populations of youth who may be at high risk for development of the disorder.
<table>
<thead>
<tr>
<th>Author(s) &amp; Date</th>
<th>Study Design &amp; Objective</th>
<th>Sampling: Size &amp; Methods, Groups</th>
<th>Variables: Independent &amp; Dependant Control &amp; Confounders</th>
<th>Tools: &amp; Diagnostic assessment approach</th>
<th>Data Collection/Time points &amp; Data Analysis</th>
<th>Internal/External Validity &amp; Strengths/Weaknesses</th>
<th>Findings/Results &amp; Authors Discussion/Conclusion</th>
<th>Author Recommendations &amp; Main contribution of the study</th>
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<tr>
<td>Andreasson et al. (1987)</td>
<td>Longitudinal Cohort Study Design</td>
<td>N=45,570 Convenience sample Military conscripts Males only (18-19 years of age)</td>
<td>IV: Cannabis use IV: SZ diagnosis Confounders controlled for: Contact with police, run away from home, fathers ETOH habits, school adjustment, socioeconomic group, smoking, solvent use, ETOH consumption, psychiatric diagnosis at conscription, medication for nervous problems, or family member on medication for nervous problems, narcotics, ETOH</td>
<td>2 Non-anonymous Questionnaires (no specific tool name provided) - 1st looked at upbringing, school &amp; personal relationships; the 2nd, use of narcotics &amp; ETOH Structured Interview (name not mentioned in this study) Psychological tests (by a trained psychologist), then ICD-8 for diagnosis (by psychiatrist) Sample was followed in the National Register for 15 years.</td>
<td>Followed in the National Register from 1969/1970-1983. Over a 15year time block Relative risk (RR) for SZ in different consumption groups calculated with 95% CI Multivariate Analysis/Logistic Model</td>
<td>Internal Validity: Tools used for assessment and diagnosis are valid and reliable Diagnostic precision External Validity: All subjects male Strengths: Assessments by trained psychologists. Large sample size Weaknesses: All males Limited information about duration of cannabis use.</td>
<td>Variable which best predicted development of SZ Relative risk (RR) for schizophrenia in high users (&gt;50x) of cannabis was 6.0 (95% CI 4.0-8.9) compared with non-users. RR=SZ was 2.4 in the group that reported use of cannabis at least once compared with non-users (95% CI 4.0-8.9). Factors correlated with ↑ occurrence of SZ independent of cannabis use: psychiatric disease other than schizophrenia at conscription; background factors (i.e. disturbed conditions of upbringing; use of solvents; &amp; poor adjustment in school, but not ETOH, smoking, or socioeconomic group). A strong association between level of cannabis consumption at conscription and admissions for drug abuse during the follow-up period was found.</td>
<td>A correlation between cannabis and SZ does not necessarily imply causation; alternately it could be that cannabis consumption might indicate an emerging SZ, therefore the relationship between cannabis and SZ should be viewed as an additional clue in the etiology of SZ. Although cannabis does ↑ the risk of SZ, it accounts for only a minority of all cases. In the vulnerability model, an individual might be vulnerable to schizophrenia but not get the disease unless it is triggered by a number of life event stressor &amp; findings suggest that cannabis use is only one may be such a stressor.</td>
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<tr>
<td>Arseneault et al. (2002)</td>
<td>Longitudinal prospective study design</td>
<td>N=759 IV: drug use at ages 15 and 18</td>
<td>Data collected from self- Baseline data at 15 &amp;</td>
<td></td>
<td>Internal Validity: Tools used were</td>
<td>SZ outcomes Cannabis users by age</td>
<td>Findings require replication in large</td>
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### Table 1: Cannabis use in adolescence as a risk factor for psychotic illness (N=7)
(see notes below for abbreviations)

<table>
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<th>Author(s) &amp; Date</th>
<th>Study Design &amp; Objective</th>
<th>Sampling: Size Methods Groups</th>
<th>Variables: Independent Dependant &amp; Confounders</th>
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<td>Objective: This is the 1st study to examine adolescent cannabis use as risk factor for adult schizophreniform disorder, taking into account childhood psychotic symptoms antedating cannabis use</td>
<td>Three groups for cannabis use at 15 &amp; 18 years: Controls n=65.1% Cannabis users @ 18yrs n=31.1% Cannabis users @ 15yrs n=3.8% No power calculation indicated in this study, but may be indicated in the original study</td>
<td>from self-reports</td>
<td>DV: assessed psychiatric symptoms at 26yrs (Psychiatric outcomes at 26 years were symptoms of SZ &amp; depression as well as diagnoses of schizophreniform disorder &amp; depression) Confounders controlled for: Psychotic symptoms at 11years (at baseline), depressive symptoms (at 26yrs), &amp; use of other drugs in adolescence</td>
<td>reports. Psychiatric symptoms at 26 assessed with a standardized interview schedule to obtain DSMIV diagnoses.</td>
<td>18years Multiple Linear Regression</td>
<td>valid and reliable (DSM-IV) Diagnostic precision External Validity: Large Sample, sample came from a larger study Strengths: Controlled for confounders (i.e. psychotic symptoms prior to drug use) Weaknesses: Did not look at drug use between the age of 11-15years Does not discuss limitations of the study</td>
<td>15years: SZ symptoms $\beta$ 6.91 (0.91) $p&lt;0.001$, schizophreniform disorder OR 4.50 (CI 95% 1.11 to 18.21) $p&lt;0.035$ Cannabis users by age 18years: SZ symptoms $\beta$ 1.04 (0.40) $p=0.009$, schizophreniform disorder OR 1.65 (0.65 to 4.18) $p=0.293$ Adding to the above (SZ outcomes) and controlling for childhood psychotic symptoms Weak psychotic symptoms at 11years: SZ symptoms $\beta$ 0.68 (0.53) $p=0.201$, schizophreniform disorder OR 4.65 (1.84 to 11.78) $p=0.001$ Strong psychotic symptoms at 11years: SZ symptoms $\beta$ 5.16 (1.39) $p=0.001$, schizophreniform disorder OR 15.97 (3.38 to 75.47) $p=0.001$ Cannabis users by 15years: SZ symptoms $\beta$ 6.56 (0.91) $p=0.001$, schizophreniform disorder OR 3.12 (0.73 to 13.29) $p=0.124$ Cannabis users by 18years: population studies with detailed measures of cannabis use &amp; schizophrenia Using cannabis in adolescence ↑ the likelihood of experiencing symptoms of SZ in adulthood. Cannabis use among psychologically vulnerable adolescents should be strongly discouraged by parents, teachers, &amp; health practitioners &amp; policy makers &amp; law makers should concentrate on delaying onset of cannabis use. These findings agree with those of the Swedish study &amp; add three new pieces of evidence.</td>
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Table 1: Cannabis use in adolescence as a risk factor for psychotic illness (N=7)
(see notes below for abbreviations)

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SZ symptoms \( \beta \) 1.03 (0.39) \( p=0.009 \), schizophreniform disorder OR 1.42 (0.54 to 3.74) \( p=0.473 \)

Adding to the above SZ outcomes and controlling for other drug use

Other drug users at 15 to 18 years: SZ symptoms \( \beta \) -0.3 (0.69) \( p=0.615 \), schizophreniform disorder OR 0.30 (0.05 to 1.62) \( p=0.160 \)

Cannabis users by 15 years: 
SZ symptoms \( \beta \) 7.2 (1.07) \( p=0.001 \), schizophreniform disorder OR 11.38 (1.84 to 70.45) \( p=0.009 \)

Cannabis users by 18 years: 
SZ symptoms \( \beta \) 1.1 (0.42) \( p=0.008 \), schizophreniform disorder OR 1.95 (0.76 to 5.01) \( p= 0.167 \)

Those who used cannabis at 15yrs were 4 x as likely be diagnosed with schizophreniform disorder at 26 than controls. After psychotic symptoms at 11 yrs were controlled for, the risk for adult schizophreniform disorder...
### Table 1: Cannabis use in adolescence as a risk factor for psychotic illness (N=7)
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<td>Zammit et al. (2002)</td>
<td>Historical Cohort Study Design Further analysis of Swedish conscripts (Andreasson et al. 1987) addresses uncertainties &amp; extends follow up to identify additional cases</td>
<td>N=50, 087 1969-70 survey of Swedish conscripts (&gt;97% of the male population aged 18-20 years) Power calculation not indicated, but sample size appears sufficiently large</td>
<td>IV: Cannabis use IV: Admission to hospital for SZ &amp; other psychoses Confounders controlled for: Other psychoactive drugs, personality traits, psychiatric diagnosis at conscription, IQ, personality variables concerned with interpersonal relationships, place of upbringing, paternal age, cigarette smoking, disturbed behaviour in childhood, hx of ETOH misuse, family hx of psychiatric illness, financial</td>
<td>Structured interviews by psychologist Those with psychiatric symptoms interviewed by psychiatrist &amp; given diagnosis according to ICD-8 Self-reports re: use of cannabis &amp; other drugs, &amp; social &amp; psychological characteristics</td>
<td>Logistic regression (95% CI) Cox</td>
<td>362/50,053 (0.71%, 95% CI 0.65% to 0.80%) subjects diagnosed with SZ by 1996. Development of SZ after conscription in subjects who used cannabis Cannabis ever: 5391 subjects total, 73 (1.4%) developed SZ, OR 2.2 (1.7 to 2.8) crude, 1.5 (1.1 to 2.0) adjusted. Frequency of use of cannabis (ever) None: 36 429 subjects total, 215 (0.6%) developed SZ Once: 608 total subjects, 2 (0.3%) developed SZ, OR 0.6 (0.1 to 2.2) crude, OR 0.6 (0.1 to 2.3) adjusted 2-4x: 1380 total subjects, 8 (0.6%) developed SZ, OR 1.0 (0.5 to 2.0) crude, 0.9 (0.4 to 1.9) adjusted 5-10x: 806 total subjects, 9 (1.1%) developed SZ, OR 1.9 (1.0 to 3.7) crude, OR 1.4 (0.7 to 2.8) adjusted 11-50x: 689 total subjects, 13 (%1.9) developed SZ, OR 3.2 (1.8 to 5.7) crude, OR 2.3 (1.5 to 3.5) adjusted. Risk ↑ in a dose dependent manner, where the largest risk was seen in subjects who reporting using cannabis &gt;50 occasions Those who used cannabis more than 50 times were at greatest risk, and the association was not accounted for by other psychological traits.</td>
<td>Cannabis is associated with ↑ risk of developing SZ in dose dependent fashion for subjects who have ever used cannabis &amp; for those who used only cannabis &amp; no other drugs. The association is not explained by use of other psychoactive drugs or personality traits.</td>
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<td>situation of the family &amp; father’s occupation</td>
<td>Retrospective re: cannabis use or psychotic symptoms (recall bias) Male only subjects</td>
<td>2.2 (1.2 to 4.0) adjusted &gt;50x: 731 total subjects, 28 (3.8%) developed SZ, OR 6.7 (4.5 to 10.0) crude, OR 3.1 (1.7 to 5.5) adjusted Adjusted ORs (95% CI) developing SZ any time after conscription for subjects taking cannabis only. None: 36,429 total subjects, 215 (0.6%) developed SZ Once: 245 total subjects, 0 developed SZ 1-4x: 499 total subjects, 5 (1%) developed SZ, OR 1.7 (0.7 to 4.2) crude, OR 1.9 (0.8 to 4.8) adjusted 5-10x: 255 total subjects, 3 (1.2%) developed SZ, OR 2.0 (0.6 to 6.3) crude, OR 1.7 (0.5 to 5.7) adjusted 11-50x: 176 total subjects, 1 (0.6%) developed SZ, OR 1.0 (0.1 to 6.9) crude, OR 0.8 (0.1 to 6.0) adjusted &gt;50x: 70 total subjects, 4 (5.7%) developed SZ, OR 10.2 (3.7 to 28.3) crude, OR 6.7 (2.1 to 21.7) adjusted. Similar results obtained when restricted to subjects developing SZ five years after conscription, to exclude symptoms.</td>
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Table 1: Cannabis use in adolescence as a risk factor for psychotic illness (N=7)  
(see notes below for abbreviations)

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<td>Ferdinand et al. (2005)</td>
<td>Cohort Study Design/ Population Health study/ Retrospective/predictive</td>
<td>N=1580 4-16 year olds Male n=1016 Female n=1060 18-30 years at time 6 Random sample</td>
<td>IV: Cannabis use DV: Future psychotic symptoms ...and vice versa IV: Psychotic symptoms DV: Cannabis use Confounders controlled for: sex, age, time</td>
<td>The composite international diagnostic interview (CIDI) Interview/ Questionnaire</td>
<td>Follow-ups over 14 years 1st data collection occurred in 1983 (T1) &amp; sample followed-up to 1997 where data collected at T6. Cox Regression Hazard ratios (HR) Regression analyses repeated to minimize recall bias</td>
<td>Internal Validity: Tools used were valid &amp; reliable Respondents answers taken at face value rather than explored by a clinician External Validity: Random selection from the general population Strengths: Large sample size Weaknesses: Retrospect can result in recall bias</td>
<td>A significant association was found (X² = 22.9, P &lt; 0.001) between life-time psychotic symptoms &amp; life-time cannabis use, although the strength of the association was small (k = 0.11, P &lt; 0.001) Cannabis use predicted psychotic symptoms HR 2.81 (95% CI = 1.79–4.43). With a requirement of minimum period of 2 years between cannabis use and onset of psychotic symptoms, the HR remained significant (2.07; 95% CI = 1.20–3.57). Mean age onset cannabis use 16.6 years. Cannabis use occurred prior to onset of psychotic symptoms in 32 &amp; average interval between cannabis use &amp; psychotic symptoms 4.6 yrs Mean age onset of symptoms 17.2 years, &amp; symptoms preceded cannabis use in 25 people.</td>
<td>My: The findings may have utility for public health policies. My: Cannabis should be discouraged by parents, teachers, and health workers. My: Prevention might lower the risk for future psychotic symptoms Cannabis use can be considered a predictor of psychosis, and alternately those who have experienced psychosis are likely to consume cannabis</td>
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Notes: prodromal cases.
Table 1: Cannabis use in adolescence as a risk factor for psychotic illness (N=7)
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<td>Henquet et al. (2004)</td>
<td>Prospective Cohort Study Design</td>
<td>N=2437 14-24years (51.3% male) Mean age 18.3 years (SD 3.3 years) at baseline &amp; 21.8 years (3.4 years) at follow up Random sampling Power calculation conducted</td>
<td>IV: Cannabis use and predisposition for psychosis DV: Psychotic symptoms at follow up Confounders: Age, socioeconomic status, urbanicity, childhood trauma, predisposition for psychosis, use of other drugs, tobacco, &amp; ETOH</td>
<td>Computer assisted method for interview Interviews by trained psychologists using the Munich version of the composite international diagnostic interview (M-CIDI).</td>
<td>Conducted over 4 years Logistic Regression</td>
<td>Internal Validity: Tools valid &amp; reliable Self-reports can present biases External Validity: Randomization of sampling method Power calculation performed to confirm sample size.</td>
<td>Cannabis use and psychosis: Any use (≥5 times); psychotic symptom at follow up 82 (19.3%) yes, 238 (11.8%) no. At least two psychotic symptoms at follow up 44 (25.3%) yes, 276 (12.2%) no. Almost daily: psychotic symptom at follow up 22 (5.2%) yes, 46 (2.3%) no. At least two psychotic symptoms 14 (8.0%) yes, 54 (2.4%) no. Predisposition for psychosis at baseline did not significantly predict cannabis use at follow up four years later (odds ratio 1.42 (95% CI 0.94 to 2.15) for the whole sample &amp;1.42 (0.88 to 2.31), for the subgroup with no cannabis use at baseline. Cannabis use at baseline ↑ the risk of developing psychotic symptoms.</td>
<td>Those who are predisposed to psychosis, have an increased risk for psychotic symptoms if they use cannabis during adolescence or young adulthood. Frequent use is associated with higher levels of risk in a dose-response fashion. Important to understand that cannabis use in young people moderately ↑ the risk of developing psychotic symptoms.</td>
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## Table 1: Cannabis use in adolescence as a risk factor for psychotic illness (N=7)

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<td>Manrique- Garcia et al. (2011)</td>
<td>Retrospective Cohort</td>
<td>The objective was to assess psychotic outcomes after cannabis use in adolescence over time. Aims: (1) Assess risk of SZ, psychosis &amp; other non-affective psychoses among cannabis users vs. nonusers (2) Examine what extent ↑ risk of schizophrenia/other psychotic outcomes over time to 55 years</td>
<td>N=50, 087 Convenience sample Swedish men conscripted during 1 year (1969–1970) for military training. Over 93% of the men were aged 18–19 years. Power calculation</td>
<td>IV: adolescent exposure to cannabis and other drugs DV: SZ, brief psychosis, other non-affective psychoses Interviews &amp; assessment conducted by psychologist Confounders controlled for: Psychiatric diagnosis at Swedish versions of ICD: ICD-8 during 1965–1986; ICD-9 during 1987–1996; &amp; ICD-10 during 1997–2007. Self-report questionnaires Interviews IQ test</td>
<td>Cox Regression Logistic Regression</td>
<td>Internal Validity: Tools valid &amp; reliable Diagnostic precision External Validity: Male subjects only Convenience sample from Swedish conscript</td>
<td>OR’s for psychotic outcomes among frequent cannabis users compared with non-users were 3.7 [95% CI (CI) 2.3–5.8] for SZ, 2.2 (95% CI 1.0–4.7) for brief psychosis and 2.0 (95% CI 0.8–4.7) for other non-affective psychoses. Very high OR for psychosis associated with drugs (21.8, 95% CI 8.3–57.0) among those with the highest consumption level was considerably reduced after adjustment (7.8, 95% CI 2.1–27.7).</td>
<td>There is a strong association between cannabis and psychotic disorders The study strengthens previous findings of association between cannabis use and psychotic disorders, &amp; clarifies issues relating to variability in risk over time, &amp; relationship between cannabis use, brief psychosis and subsequent onset of SZ.</td>
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<td>Stephanis et al. (2013)</td>
<td>Retrospective Cohort Design</td>
<td>N=997 Estimated resident population 18–64 years</td>
<td>Participants were from the 2010 Survey of High Impact Psychosis (SHIP) in Australia Random selection</td>
<td>IV: Age of initiation of cannabis (AIC) DV: Age of psychosis (AOP) AOP is defined to the nearest year, and was the earliest age that medical advice was sought. Control variable: Depression Confounders controlled for: Family hx of SZ &amp; psych disorders, substance use-</td>
<td>Interviews conducted by a trained interviewer DIP: standardized semi-structured interview for diagnosis of psychosis (comparable with DSM IV and ICD 10) Survey OPCRIT diagnostic computer algorithm</td>
<td>Univariate General Linear Models Internal Validity: Tools valid &amp; reliable. Interviews conducted by trained interviewers. Inter- rater reliability χ=94 Potential recall bias External Validity: Random sample Strengths: Large sample Random sample Weaknesses: Effect of AIC on AOP was significant, $F(8,978) = 25.37, P &lt; .001$, adjusted $R^2 = 0.19$. Effect of sex was not significant, $F(1,977) = 2.02, P = .16$. Effect of AIC on AOP remained significant after family history of SZ or other psychiatric disorders was used as covariate, $F(11, 984) = 13.77, P &lt; .001$, $R^2 = 0.20$. Using the Curve Estimation procedure (to examine which regression model best fit to the data), 3 models were tested (linear, cubic, and quadratic). It was found that a linear model of association</td>
<td>Cannabis may exert a cumulative toxic effect on individual’s pathway to developing psychosis. The manifestation of AOP might be delayed for ~7–8 years regardless of AIC Largest study to examine the effects of AIC use in psychotic disorders.</td>
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<td>(ETOH, tobacco, cannabis, LSD, cocaine, ecstasy &amp; heroine)</td>
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<td>Retrospective nature can present recall bias</td>
<td>provided a better fit to the data, $F(1,994) = 224.32$, $P &lt; .001$ For the entire sample the effect of AIC on DPEC was not significant, $F(8,988) = 1.28$, $P = .25$, adjusted $R^2 = 0.002$, for trend $F(8,988) = 0.944$, $P = .33$. Mean DPEC for the entire SHIP sample was 7.85 ($SD = 6.2$) years AIC is directly and linearly associated with AOP with an average delay of 7–8 years (mean 7.85, $SD = 6.2$) from 1st exposure to cannabis.</td>
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Note: AOP=Age at onset of psychotic illness, AIC=Age at initiation of cannabis use, DV=Dependent Variable, ETOH=alcohol, Hx=History, IV=Independent Variable, RR=Relative Risk, SZ=Schizophrenia.
**Table 2. Impact of adolescent cannabis use on neurodevelopment (N=5)**

(see notes below for abbreviations)

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<td>Peters et al. (2009)</td>
<td>Case-control study design</td>
<td>N=56, n= 35 male recent-onset SZ patients, with &amp; without a hx of cannabis use before 17 years, n=21 matched healthy comparison men without illicit drug use</td>
<td>IV: Adolescent cannabis use in adolescent onset SZ DV: White matter abnormalities Confounding variables: None excluded Controls: Healthy subjects</td>
<td>MRI performed &amp; evaluated by neuro-radiologist</td>
<td>Adolescent cannabis use and hard drug use on FA were tested correlational &amp; categorical</td>
<td>Internal Validity: Matched controls Tools used were valid and reliable Trained residents psychiatrists for diagnosis Diagnostic precision</td>
<td>The repeated-measures ANOVA for cannabis use before 17yrs showed a significant effect of group (F= 6.0, df =2, p =0.005). Follow-up ANOVA’s revealed significant differences between groups in the anterior internal capsule (F =5.0, df =2, p =0.01), fasciculus uncinate (F=11.1, df =2, p = 0.001) and frontal white matter (F=5.2, df=2, p=0.009)</td>
<td>Those who use cannabis in adolescence may present with in ↑ WM which may reflect structural hyperconnectivity, in contrast to other DTI studies. Further studies are necessary to assess the effect of adolescent cannabis and other illicit drug use on brain WM in SZ Abnormalities were absent in patients without cannabis use before age 17.</td>
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<td>James et al. (2011)</td>
<td>Observational/Descriptive Case-control Design To study cognitive and</td>
<td>N=32, n=16 AOS subjects (11 males, 5 females, aged 13 to 18 years) positive</td>
<td>IV: Cannabis use in adolescent onset schizophrenia (AOS) DV:</td>
<td>DSM IV K-SADS-PL PANSS Family hx ascertained using Family History Research Diagnostic</td>
<td>General Linear Model ANCOVA</td>
<td>Internal Validity: Tool (MRI) used was valid and reliable Matched sample</td>
<td>Total white matter (Mean ± SD): Control subjects: 816.618 ± 61.375 AOS non-cannabis users: 798.003 ± 54.878 AOS cannabis users: 827.238 ± 61.380 Total grey matter (Mean ± SD) Control subjects: 885.491 ± 53.416</td>
<td>Further work on effects of cannabis on targeted pathways around the critical period of puberty is warranted, particularly in view</td>
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Table 2. Impact of adolescent cannabis use on neurodevelopment (N=5)  
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<td>Solowij et al. (2011)</td>
<td>Cross-sectional Design</td>
<td>N=48 n=17 patients with SZ n=31 healthy controls recruited; 48% healthy &amp; 47% long-term heavy cannabis use.</td>
<td>DI: cannabis users (with and without SZ) Referrals from psychiatrists &amp; SZ research bank SANS SAPS Hamilton depression rating scale GAF MRI</td>
<td>Cerebellar measures extracted from (MRI) scans using semi-automated methods ANCOVA Correlational analyses.</td>
<td>Internal Validity: Tools used were valid and reliable External Validity: Male sample only Strengths: Matched control sample Weaknesses: Male sample group</td>
<td>ANCOVA with current levels of ETOH &amp; tobacco use as covariates determined a significant overall difference between the four groups in WM volume [F(3, 38)=4.23, p=0.011], but groups did not differ in GM [F(3, 38)=0.55, p=0.65] or total cerebellar volume [F(3, 42)=1.68, p=0.19]. Whole-brain WM volume did not differ between groups [F(3, 42)=0.58, p=0.63] and its inclusion as a covariate in the analysis of cerebellar WM volume did of its role in schizophrenia and its wide-spread use. The pattern of loss of GM density in AOS is thought to reflect synaptic pruning &amp; increasing myelination, &amp; is likely an exaggeration of normal maturation</td>
<td>ANCOVA non cannabis users: 858,441 ± 56,264 AOS cannabis users: 849,595 ± 56,889 Volumetric analysis of subcortical gray structures showed no group difference (MANOVA, Pillai trace=0.217, F=0.89, df.=14, p=0.57) between control and AOS Volumetric analysis of subcortical gray structures showed no group difference (MANOVA, Pillai trace=0.41, F=0.85, d.=14, p=0.61) between CAN+ve and CAN−ve subjects. Overall, compared to CAN−ve subjects, CAN+ve subjects showed GM density loss. The CAN+ve patients had a later onset of psychosis (p=0.04) than CAN−ve patients</td>
<td>The primary finding of this study is of significantly smaller cerebellar WM volume in cannabis users compared to non-users, with the greatest reduction relative to healthy controls evident in SZ patients with co-morbid cannabis</td>
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<td>Age range: 21–60 years (with consumption of cannabis daily from 9-32 years)</td>
<td>tobacco</td>
<td>Pearson product-moment correlations for normally distributed data</td>
<td>Spearman rank order correlations for skewed data</td>
<td>not alter the significant overall group difference [F(3, 37)=3.70, p=0.02].</td>
<td>Cerebellar WM volume was reduced in cannabis users with and without SZ compared to healthy non-users.</td>
<td>The THC group did not differ in WM volume from either of the schizophrenia groups (SZ+THC: p=0.45; SZ – THC: p=0.45).</td>
<td>An overall interaction between SZ diagnosis and cannabis use status did not reach significance for WM volume [F(1, 38)=1.15, p=0.29], but the main effect of cannabis use (regardless of diagnosis) was highly significant [F(1, 38)=7.76, p=0.008]. The main effect of diagnosis (SZ versus healthy sample regardless of cannabis use) was also significant [F(1, 38)=4.31, p=0.045].</td>
<td>Healthy cannabis users did not differ in WM volume from either of the schizophrenia groups.</td>
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<td>Cohen et al. (2012)</td>
<td>Cross-sectional Design</td>
<td>N= 55&lt;br&gt;Control n=19 Young cannabis users n=17, non-using n=13 cannabis using FES outpatients n=6&lt;br&gt;Convenience sample&lt;br&gt;Recruited through community advertisement&lt;br&gt;Age at onset of THC use (S.D.): Cannabis-using subjects 15.1 yrs (2.4), Cannabis-using FES 15.5 yrs (2.3)</td>
<td>IV: young cannabis users, non-using and using first episode psychosis patients&lt;br&gt;4 different groups in total (including the control)</td>
<td>MRI&lt;br&gt;DSM IV for diagnosis</td>
<td>Demographic data were compared between groups by non-parametric testing for nominal data or one way ANOVA&lt;br&gt;Pearson’s Correlation coefficients</td>
<td>Internal Validity: Diagnostic tools are valid and reliable&lt;br&gt;External Validity: Small sample size, so generalizability is limited&lt;br&gt;Convenience sample Strengths: Cortical pattern matching&lt;br&gt;Matched for age, handedness, gender, cannabis use and duration of illness&lt;br&gt;Weaknesses: The study is limited by sample size</td>
<td>Age at onset of cannabis use correlated with years of use (r=0.52, p=0.03) which, in turn, correlated with total individual lifetime doses (r=0.58, p=0.01).&lt;br&gt;GM reduction was confirmed for three lobules as dependent on the three parameters describing the pattern of cannabis use history (lobule III : F3,16= 4.4, p=0.02; lobule IV: F3,16=4.7, p=0.02 ; lobule V: F3,16=4.6, p=0.02) with total lifetime doses significantly predicting GM reduction in these lobules (lobule III : b=x0.63, t=x2.6, p=0.02; lobule IV: b=x0.74, t=x3.1, p&lt;0.01 ; lobule V: b=x0.52, t=x2.2, p&lt;0.05).&lt;br&gt;Age at onset of cannabis use also showed a statistically non-significant trend towards being associated with GM reduction in lobule III (b=x0.46, t=x2.0, p&lt;0.07)&lt;br&gt;FES subjects also showed greater total white-matter volume (p=0.03) and lower total grey: total cerebellar volume ratio (p=0.007) than healthy controls</td>
<td>This is the first study to link cerebellar pathology to juvenile cannabis use by employing cortical pattern matching&lt;br&gt;Structural changes can be seen in brain morphology when cannabis is used during adolescence.&lt;br&gt;Irrespective of cannabis use, there is observed pathology with SZ patients.</td>
</tr>
</tbody>
</table>
Table 2. Impact of adolescent cannabis use on neurodevelopment (N=5)
(see notes below for abbreviations)

<table>
<thead>
<tr>
<th>Author(s) &amp; Date</th>
<th>Study Design</th>
<th>Objective</th>
<th>Sampling: Size Methods &amp; Groups</th>
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<th>Findings/ Results &amp; Authors Discussion/ Conclusion</th>
<th>Authors/My Recommendations &amp; Main contribution of the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kumra et al. (2012)</td>
<td>Observational/ Descriptive Cross-sectional Design</td>
<td>This study characterized cerebral cortical gray matter structure in adolescents in regions of interest (ROIs) that have been implicated in EOS and cannabis use disorders (CUD).</td>
<td>N=115 10-21 years Recruited from clinical programs U of Minnesota. EOS (n=35), CUD (n=16), EOS/CUD (n=13), &amp; healthy controls (HC) (n=51) EOS subjects: schizophrenia (n=38), schizoaffective (n=3), or schizophréniform disorder (n IV: Adolescents with early onset schizophrenia and with cannabis use disorder, those with both EOS and CUD, and healthy controls DV: Gray matter structure in regions of interest</td>
<td>Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version or the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) using multiple data sources. DSM diagnosis (substance/ETOH use) SCID DSM for schizophrenia Time line follow</td>
<td>regression two-way ANOVA</td>
<td>Post hoc pairwise group comparisons ANCOVA MANCOVA Spearman rank correlations Controlled for age, sex, and WRAT reading scores.</td>
<td>Internal Validity: Tool (MRI) valid and reliable Controlled for confounders External Validity: Sample size small, non-random Strengths: Controlled for confounders Weakness: Majority of EOS pts were being treated with antipsychotic medication at the time of the MRI examination.</td>
<td>MANCOVA showed no significant main effect for either SZ (F48,60=1.34, p =.14) or cannabis use disorder (F48,60 =1.33, p=.15), but a significant overall cannabis use disorder-by-diagnostic group interaction (F48,60 =1.88, p=.01) For cortical thickness, the MANCOVA revealed no significant main effect for schizophrenia (F7,101 =1.54, p =.15) or cannabis (F7,101 =0.85, p=.55) and there was no significant cannabis by-diagnostic group interaction (F7,101 =0.82, p=.58). For cortical surface area, MANCOVA revealed no significant main effect for schizophrenia (F7,101 =0.78, p =.61) or cannabis (F7,101 =0.45, p = .87), but a significant overall cannabis-by-diagnostic group interaction (F7,101 = 3.41, p =.003). ANCOVA revealed significantly lower three-digit d= scores on the CPT –</td>
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<tr>
<td>My: This info would be important to share with the public, and particularly those who work in MH &amp; adolescents</td>
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(see notes below for abbreviations)

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<th>Authors/My Recommendations &amp; Main contribution of the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>CUD recruited from tx settings for dependency. n=51 healthy controls (HC) recruited from the same area</td>
<td>=7) &amp; reported onset of psychosis prior to 18 years.</td>
<td>back for information about cannabis use Drug urine screen</td>
<td>IP (indicating worse performance) (F3,112 =12.3, p=.001) for adolescents with schizophrenia (EOS: mean =1.56, SD =0.89) compared with HC subjects (mean =2.78, SD =.93) and nonpsychotic adolescents with CUD (mean =2.47, SD= 0.90) controlling for age, sex, and WRAT reading scores.</td>
<td>In the left superior parietal region, &quot;pure&quot; EOS and &quot;pure&quot; CUD had smaller gray matter volumes associated with lower surface area compared with HC. The co-morbid group had smaller gray matter volumes compared with CUD and HC groups. Presence of CUD may moderate the relationship between EOS and cerebral cortical GM structure in the left superior parietal lobe.</td>
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</tbody>
</table>

Note: AOS=Adolescent onset schizophrenia, CAN+ve=Cannabis using, CAN-ve=Cannabis non-using, CUD=Cannabis use disorder, EOS=Early onset Schizophrenia, GM=Grey matter, Increase(d)=↑, WM=White matter
Table 3. How genetics/epigenetics relate to the onset of psychosis in adolescents who use cannabis (N=1)
(see notes below for abbreviations)

<table>
<thead>
<tr>
<th>Author(s) &amp; Date</th>
<th>Study Design &amp; Objective</th>
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<th>Authors/My Recommendations &amp; Main contribution of the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrada et al. (2011)</td>
<td>Cross-sectional Design</td>
<td>N=157 Young Caucasian psychiatric inpatients, Mean age 17.01 years (SD = 3.6)</td>
<td>Two variables of cannabis use considered for analyses: i) lifetime cannabis use or non-cannabis use &amp; ii) age at first cannabis use</td>
<td>Blood testing and buccal swab for DNA Age at onset was defined as the age at first psychiatric admission</td>
<td>Data was collected about drug use, age at first use &amp; frequency of psychoactive drugs, UDS performed, &amp; DNA.</td>
<td>Internal Validity: Tools were valid &amp; reliable External Validity: Equal opportunity Convenience (consecutive) sampling Strengths: Equal opportunity Convenience (consecutive) sampling</td>
<td>Age at first cannabis use correlated with age at onset of psychiatric disorders, in both the schizophrenia spectrum disorders group (b = 1.59 SE = 0.27 P &lt; 0.001) and in the other psychiatric disorders group (b = 0.40 SE = 0.14 P = 0.006). The Val158Met genotype showed an effect on age at onset in cannabis users with a schizophrenia-spectrum disorder (b = 1.66 SE = 0.78 p = 0.04) When tested whether the age at onset of psychiatric disorders was influenced by the interaction between COMT Val 158 Met genotype &amp; the age at first cannabis use, a marginally significant effect appeared in schizophrenia-spectrum disorder group (b = 0.93 SE = 0.46 P = 0.05). Those who started using cannabis earlier had an earlier age at onset of psychiatric disorders. Val 158 Met genotypes were no different between diagnosis groups (SZ, non-SZ) or cannabis users and non-users. An interaction between Val158Met genotypes &amp; cannabis use was observed specifically on age at emergence of psychotic disorders, with Val⁄Val genotype carriers showing an earlier age at onset than Met carriers.</td>
<td>More observational research with larger samples is needed This study provides further evidence that age at first cannabis use modifies the age at onset of both psychotic and non-psychotic disorders. The results from this study suggest the importance of brain maturation timing in which exposure to cannabis occurs. The COMT Val158Met genotype seems to modulate the association between cannabis and age at onset of psychotic disorders. These results are consistent with previous studies.</td>
</tr>
</tbody>
</table>

Note: COMT=Catechol-O-methyl transferase, Met=Methionine, Val=Valine
## A.4. Table 4. Childhood trauma as a risk factor for psychotic symptoms in adolescents who use cannabis N=3

(see notes below for abbreviations)

<table>
<thead>
<tr>
<th>Author(s) &amp; Date</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Houston et al. (2008)</td>
<td>Epidemiological Cohort Study Design</td>
<td>N=5877 Large, nationally represented community sample</td>
<td>IV: Sexual Abuse, Early Cannabis Use DV: Psychosis Confounders: 1st block: sex, age, urbanicity, ethnicity, depression, education, employment, living arrangements 2nd block: cannabis use and sexual trauma and the cannabis use &amp; sexual trauma interaction</td>
<td>CIDI used to assess lifetime prevalence of non-affective psychosis (SZ, schizophréniform disorder, schizoaffective disorder, delusional disorder, &amp; atypical psychosis), information relating to cannabis use, and information relating to childhood sexual traumas Diagnosis of psychosis was based on re-interviews by experienced clinicians using an adapted version of the Structured Clinical Interview for the DSM-III-R</td>
<td>Used a Hierarchical Binary Logistic Regression Model</td>
<td>Internal Validity: Assessment/diagnostic tools both valid and reliable External Validity: Large sample size and national representation makes the findings generalizable Strengths: Controlled for many potential confounding factors identified as risk factors for psychosis in other studies. Weaknesses: Underestimate of abuse</td>
<td>First used cannabis under 16 yrs n=643, raped +cannabis under 16 yrs n=143, molested +cannabis under 16 yrs n=469, any sexual trauma under 16 yrs n=543 The first block of the regression model was significant (x² = 88.27, df = 8, P = .00) The main effects for cannabis and trauma were not significant, but the interaction was statistically significant. The effect for sexual trauma was statistically significant for those who used cannabis &lt; 16 yrs (OR = 11.96, 95% CI = 2.10 – 68.22, P = .01) but not for those who had not used cannabis &lt; 16 yrs (OR = 1.80, 95% CI = 0.91 – 3.57, P = .09). Further research is necessary in order to demonstrate the robustness of this finding. It would be valuable to establish if different temporal ordering of cannabis use and trauma was associated with different risks of psychosis. For example, it may be that exposure to a trauma followed by cannabis use (self-medication) &amp; cannabis use followed by trauma produce different likelihoods of psychosis. The mediating role of cannabis suggests that early cannabis use may increase the strength of the proposed trauma-psychosis relationship</td>
<td></td>
</tr>
</tbody>
</table>

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**A.4. Table 4. Childhood trauma as a risk factor for psychotic symptoms in adolescents who use cannabis N=3**

(see notes below for abbreviations)

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<th>Authors/My Recommendations &amp; Main contribution of the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harley et al. (2010)</td>
<td>Population based Study Design</td>
<td>To investigate whether the presence of both childhood trauma and early cannabis use increases the risk of experiencing psychotic symptoms in adolescence beyond that expected if each risk factor were working independently.</td>
<td>N=211 Adolescents 12-15 years &amp; their parents Stratified random sampling No power calculation conducted</td>
<td>IV: the presence of childhood trauma DV: Psychotic symptoms Confounder: Gender and school</td>
<td>Psychiatric interviews using the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) semi-structured instrument for diagnosis of Axis I according to DSM IV Strengths and Difficulties Questionnaire (SDQ) Children’s Depression Inventory (CDI)</td>
<td>Stratified our data into four categories: (1) no exposure to cannabis use or childhood trauma [R], (2) exposure to cannabis use only [R(A)], (3) exposure to childhood trauma only [R(B)], and (4) exposure to both cannabis use and childhood trauma [R(AB)]. ORs</td>
<td>Logistic regression</td>
<td>Internal Validity: Tools used were valid and reliable</td>
</tr>
</tbody>
</table>
A.4. Table 4. Childhood trauma as a risk factor for psychotic symptoms in adolescents who use cannabis N=3
(see notes below for abbreviations)

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<tr>
<td>Mackie et al. (2013)</td>
<td>Longitudinal prospective population study Design</td>
<td>Convenience sample Obtained from 8 secondary schools in Greater London Schools were initially recruited N=1098 Follow up: T2 n=851 T3 n=988 T4 n=897 T5 n=843</td>
<td>IV: bullying &amp; cannabis use DV: onset of psychotic symptoms (&amp; where transitory experiences to become abnormally Persistent) Confounders: Other illicit drug use Controls: Cannabis use, bullying</td>
<td>Self-reports Five questions about psychosis were adapted from the Diagnostic Interview Schedule Two items from the Reckless Behavior Questionnaire (Shaw et al. 1992) assessed the frequency of cannabis and other illicit drug use</td>
<td>Over 5 time periods, separated by 6 mos, and over 24 months in total Multi-nominal Logistic Regressions</td>
<td>Under reporting on sexual abuse may have occurred. The original study was designed as an epidemiological study of mental health in adolescents, not specifically to test these hypotheses</td>
<td>Individuals who experienced bullying 1-2 x/month were 2.37 times [95% confidence interval (CI) 1.25–4.52] as likely to report elevated psychotic experiences and 1.67 times (95% CI 0.97–2.86) as likely to report increasing psychotic experiences. Those who experienced bullying &gt;3x/month were 3.43 times (95% CI 1.82–6.46) as likely to report increasing psychotic experiences. Those who reported cannabis use onset prior to age 14 were 2.54 (95% CI 1.22–5.23) and 2.16 (95% CI 1.20–3.90) times as likely to report elevated &amp; increasing psychotic experiences respectively Those who reported cannabis use only</td>
<td>Assessments of bullying &amp; cannabis use can be used in interviews and/or assessments Previous research focused on an association between environment &amp; future psychotic experiences at one time point whereas these findings include change over time. Further research would allow for early detection and thus intervention</td>
</tr>
</tbody>
</table>
A.4. Table 4. Childhood trauma as a risk factor for psychotic symptoms in adolescents who use cannabis N=3
(see notes below for abbreviations)

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</tr>
</thead>
<tbody>
<tr>
<td>environmental risk factors with developmental pattern.</td>
<td>for another study</td>
<td>Mean age 13.6 years</td>
<td>60.9% boys 39.1% girls</td>
<td>No power calculation performed</td>
<td>Olweus Bully/Victim Questionnaire Depression subscale from the self-report Brief Symptom Inventory</td>
<td></td>
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<td>once revealed 1.90 times (95% CI 1.00–3.73) as likely to report increasing psychotic experiences, &amp; adolescents reporting cannabis use two or more occasions were 2.33 times (95% CI 1.25–3.96) more likely to report elevated psychotic experiences. Those who did not experience bullying or cannabis use &amp; those who experienced only one risk factor were 1.79 times (95% CI 1.00–3.22) as likely to report increasing psychotic experiences. Those who experienced both risk factors were 2.92 times (95% CI 1.45–5.78) and 2.09 (95% CI 1.20–3.58) times as likely to report elevated or ↑ psychotic experiences.</td>
</tr>
</tbody>
</table>
References


doi:10.1017/S0033291711002078


Appendices

APPENDIX A: STROBE Statement—checklist of items that should be included in reports of observational studies

<table>
<thead>
<tr>
<th>Item No</th>
<th>Title and abstract</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| 1       | (a) Indicate the study’s design with a commonly used term in the title or the abstract  
         | (b) Provide in the abstract an informative and balanced summary of what was done and what was found |
| 2       | Introduction                        |                |
| 2       | Background/rationale                | Explain the scientific background and rationale for the investigation being reported |
| 3       | Objectives                          | State specific objectives, including any pre-specified hypotheses |
| 4       | Methods                             |                |
| 4       | Study design                        | Present key elements of study design early in the paper |
| 5       | Setting                             | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection |
| 6       | Participants                        |                |
| 6       | (a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up  
         | Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls  
         | Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants  
         | (b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed  
         | Case-control study—For matched studies, give matching criteria and the number of controls per case |
| 7       | Variables                           | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable |
For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.

Describe any efforts to address potential sources of bias.

Explain how the study size was arrived at.

Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why.

(a) Describe all statistical methods, including those used to control for confounding.

(b) Describe any methods used to examine subgroups and interactions.

(c) Explain how missing data were addressed.

(d) *Cohort study*—If applicable, explain how loss to follow-up was addressed.

*Case-control study*—If applicable, explain how matching of cases and controls was addressed.

*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy.

(e) Describe any sensitivity analyses.

(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed.

(b) Give reasons for non-participation at each stage.

(c) Consider use of a flow diagram.

(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders.

(b) Indicate number of participants with missing data for each variable of interest.

(c) *Cohort study*—Summarise follow-up time (eg, average and total amount).

*Case-control study*—Report numbers of outcome events or summary measures over time.

*Case-control study*—Report numbers in each exposure category, or summary measures of exposure.
**Cross-sectional study**—Report numbers of outcome events or summary measures

| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included  
(b) Report category boundaries when continuous variables were categorized  
(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Other analyses</td>
<td>17</td>
<td>Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses</td>
</tr>
</tbody>
</table>

| **Discussion** |
| --- | --- |
| Key results | 18 | Summarise key results with reference to study objectives |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results |

| **Other information** |
| --- | --- |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
## APPENDIX B: Examination of Studies based on STROBE Statement Checklist

<table>
<thead>
<tr>
<th>GROUPS:</th>
<th>Cannabis use in adolescence as a risk factor for psychotic illness</th>
<th>Impact of adolescent cannabis use on neurodevelopment</th>
<th>How genetics/epigenetics relate to the onset of psychosis in adolescents who use cannabis</th>
<th>Childhood trauma as a risk factor for psychotic symptoms in adolescents who use cannabis</th>
</tr>
</thead>
<tbody>
<tr>
<td>STUDIES: No.</td>
<td>1 2 3 4 5 6 7</td>
<td>8 9 10 11 12</td>
<td>13</td>
<td>14 15 16</td>
</tr>
</tbody>
</table>

### STROBE Criteria:

#### TITLE/ABSTRACT:
- Study design is clearly indicated in the title and/or abstract.  
  - Y Y Y Y Y Y N N N N N N N N N Y Y
- The abstract provided information on what was done & found  
  - Y N Y Y Y Y Y Y Y Y Y Y Y Y

#### INTRODUCTION:
- Background & rationale provided.  
  - Y N Y Y Y Y Y Y Y Y Y Y Y Y
- Objectives/hypothesis clearly stated  
  - Y Y Y Y Y Y Y Y Y Y Y Y Y Y

#### METHODS:
- Study design  
  - Y N Y Y Y Y N N N N N N N N IC IC Y
- Key elements of study design presented early in the paper  
  - Y N Y Y Y Y Y Y Y Y Y Y IC IC Y
- Setting  
  - Indicates location, dates, recruitment, exposure, follow-up, & data collection  
  - Y N Y Y Y Y Y Y Y Y IC IC Y Y

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<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Participants</td>
<td></td>
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</tr>
<tr>
<td>i). Cohort study—Gives eligibility criteria, sources &amp; methods of selection, &amp; methods of follow-up;</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Case-control study- (same as above) &amp; also provides rationale for choices of cases &amp; control selection;</td>
<td>-</td>
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<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cross-sectional study-(same as above)</td>
<td>-</td>
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<tr>
<td>ii). Cohort study—For matched studies, gives matching criteria &amp; number of exposed and unexposed</td>
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<td>-</td>
</tr>
<tr>
<td>Case-control study—For matched studies, gives matching criteria (as above), &amp; number of controls per case</td>
<td>-</td>
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<td>-</td>
</tr>
<tr>
<td>Variables</td>
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</tr>
<tr>
<td>Defines outcomes, exposure, predictors, potential</td>
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<td>Y</td>
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<td>STUDIES:</td>
<td>No.</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>confounders, &amp; effect modifiers &amp; diagnostic criteria if applicable.</td>
<td></td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Data sources/Measurement</td>
<td></td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
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<tr>
<td>Bias</td>
<td></td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Efforts to address potential bias</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Study Size</td>
<td></td>
<td>N</td>
<td>N</td>
<td>N</td>
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<tr>
<td>How the study size was arrived at, &amp;/or power calculation</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Quantitative Variables</td>
<td></td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Explains how variables were analysed &amp; if applicable, describes which groupings were chosen and why</td>
<td></td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Statistical Methods i). Describes statistical</td>
<td></td>
<td></td>
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</tbody>
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APPENDIX B: Examination of Studies based on STROBE Statement Checklist
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<tr>
<td>methods, including those used to control for confounding</td>
<td></td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>ii). Describes methods used to examine subgroups &amp; interactions</td>
<td></td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>iii). Explains how missing data were addressed</td>
<td></td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>iv). Cohort study-If applicable, explains how loss to follow-up was addressed</td>
<td></td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Case-control study-If applicable, explains how matching of cases and controls was addressed</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cross-sectional study-If applicable, describes analytical methods taking account of sampling strategy</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>v.) Describes sensitivity analyses</td>
<td></td>
<td>N</td>
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<td>8 9 10 11 12</td>
<td>13</td>
<td>14 15 16</td>
</tr>
<tr>
<td>RESULTS:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>i). Reports numbers of individuals during stages of study – i.e. eligibility, follow-up, &amp; those analysed</td>
<td>[N N Y Y Y Y Y Y Y Y Y Y Y N N N N Y]</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ii). Gives reasons for non-participation at each stage</td>
<td>[Y N N N N Y N N N N N N N N Y]</td>
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<tr>
<td>iii). Uses a flow diagram</td>
<td>[Y N N N N N N N N N N N N N N]</td>
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</tr>
<tr>
<td>Descriptive data</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>i). Gives characteristics of study participants (e.g. demographic, clinical, social) and info on exposures &amp; potential confounders</td>
<td>[Y Y Y Y Y Y Y Y Y Y Y Y Y N]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ii). Indicates number of participants with missing data for the variables of interest</td>
<td>[Y N N N N Y N N N N N N N N N]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>iii). Cohort study– summarises follow-up time (e.g., average and total)</td>
<td>[Y Y Y Y Y Y - - - - - - - - N N N Y]</td>
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<td>4</td>
</tr>
<tr>
<td>Outcome data&lt;br&gt;<strong>Cohort study</strong> - Reports numbers of outcome events or summary measures over time</td>
<td>-</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
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<tr>
<td><strong>Case-control study</strong> - Reports numbers in each exposure category, or summary measures of exposure</td>
<td>N</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Cross-sectional study</strong> - Reports numbers of outcome events or summary measures</td>
<td>N</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Main results&lt;br&gt;i). Gives unadjusted estimates &amp; if applicable, confounder-adjusted estimates/precision (e.g., 95% CI). Makes clear which confounders were adjusted for &amp; why</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
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<td>ii). Reports category boundaries when continuous variables were categorized</td>
<td>-</td>
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<tr>
<td>iii). If relevant, considers translating estimates of relative risk into absolute risk for a meaningful time period</td>
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<tr>
<td>Other analyses</td>
<td>Y  Y  Y  Y  Y  Y  Y  Y  Y  Y  Y  Y  Y  Y  Y</td>
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<tr>
<td>Reports other analyses done- e.g. analyses of subgroups, interactions, &amp; sensitivity analyses</td>
<td>Y  Y  Y  Y  Y  Y  Y  Y  Y  Y  Y  Y  Y  Y  Y</td>
<td></td>
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**DISCUSSION:**
- Key results
- Summarises key results with reference to study objectives
- Limitations
- Discusses limitations, taking into account sources of potential bias/imprecision.
- Discusses direction & magnitude of potential bias
- Interpretation
- Gives results, considers objectives, limitations, multiple analyses, results from similar studies, & other
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<td>evidence</td>
<td></td>
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<tr>
<td>Generalizability/(External validity)</td>
<td>N N N N Y/N N N N N N Y Y/N N</td>
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</tr>
<tr>
<td>OTHER INFORMATION: Funding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Funding source, role of funders &amp; original study that the article is based</td>
<td>Y Y Y N Y Y Y N Y Y Y Y Y N Y Y</td>
<td></td>
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Note: IC=Incomplete, N =No, Y =Yes, N/A=Not Applicable Symbols: (-) design not appropriate

References

(Arranged by study table groups and chronologically)

Table 1: Cannabis use in adolescence as a risk factor for psychotic illness


**Table 2: Impact of adolescent cannabis use on neurodevelopment**


Table 3: How genetics/epigenetics relate to the onset of psychosis in adolescents who use cannabis


Table 4: Childhood trauma as a risk factor for psychotic symptoms in adolescents who use cannabis

