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CANNABIS, SCHIZOPHRENIA AND OTHER PSYCHOSES: LONGITUDINAL STUDIES ON SWEDISH CONSCRIPTS

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LONGITUDINAL STUDIES ON SWEDISH CONSCRIPTS

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Con mucho cariño para mis queridos

padres que siempre me han apoyado

Jose Epimenio Manrique Mora

y Graciela Garcia de Manrique

ABSTRACT

AIM

The overall aim of this thesis was to investigate the association between cannabis use and psychiatric disorders with emphasis on schizophrenia, other psychoses, depression and long term effects on mortality. Specific objectives were to: 1) investigate the long-term risk of schizophrenia, and other psychoses including brief psychoses among users and non-users of cannabis, (2) assess the risk of depression among users and non-users of cannabis, (3) determinate whether schizophrenia patients with a history of cannabis use have a different prognosis, with regards to readmission and hospital duration, compared with those without a history of cannabis use, (4) assess the overall risk of death among cannabis users compared with non-users; and assess mortality among persons with psychotic disorders and find out to what extent cannabis use affects the excess mortality

METHODS

A Swedish cohort of 50 087 military conscripts with data on cannabis use recorded in 1969 was followed up until 2007 (Study I, II, and III), and until 2011 (Study IV) in the Swedish National Patient Register and the Cause of Death Register as well as other socio-demographic databases. Information on a number of possible confounders were derived from the Swedish conscription cohort in 1969. Different statistical methods (cox proportional hazards models, negative binomial regression, logistic regression, multinomial logistic regression, and Fisher's exact test) were used in this thesis.

RESULTS

(1) Heavy cannabis users remain with a higher risk of schizophrenia throughout the follow-up period compared to non-users. (2) After control for confounding factors and especially markers of disturbed behaviour during childhood, there was no increased risk of future depression among cannabis users. (3) Schizophrenia patients with a history of cannabis use had a significantly higher burden of in-patient care, with regard to hospital readmission and hospital duration, compared with those without a history of cannabis use. (4) Subjects with a history of heavy cannabis use are at higher risk of death compared with non-users. A history of cannabis use did not affect the increased mortality among persons with psychotic disorders.

CONCLUSIONS

It seems like the association between cannabis and schizophrenia may be stronger than that between cannabis and other psychiatric disorders such as brief psychosis and depression. Our findings indicate that the course and prognosis of schizophrenia may be more severe in cannabis users than schizophrenia cases in general. Subjects with a history of heavy cannabis use are at higher risk of long term psychotic effects as well as early death compared with non-users.

LIST OF SCIENTIFIC PAPERS

I. **Manrique-Garcia E**, Zammit S, Dalman C, Hemmingssond T, Andreasson S, Allebeck P. Cannabis, schizophrenia and other non-affective psychoses: 35 years of follow-up of a population-based cohort. Psychological Medicine. 2012;42(6):1321-8

II. **Manrique-Garcia E**, Zammit S, Dalman C, Hemmingssond T, Allebeck P. Cannabis use and depression: a longitudinal study of a national cohort of Swedish conscripts. BMC Psychiatry. 16;12:112

III. **Manrique-Garcia E**, Zammit S, Dalman C, Hemmingssond T, Andreasson S, Allebeck P. Prognosis of schizophrenia in persons with and without a history of cannabis use. Psychological Medicine. 2014; 44(12):2513-21

IV. **Manrique-Garcia E**, Dalman C, Andreasson S, Allebeck P. Cannabis, psychosis and mortality: a cohort study of 50 087 Swedish men [manuscript].

CONTENTS

LIST OF ABBREVIATIONS

CB1	Cannabinoid receptor type 1
DSM	Diagnostic and Statistical Manual of Mental Disorders
ICD	International Classification of Diseases
THC	Delta-9-tetrahydrocannabinol

1 Background

1.1 Cannabis

Cannabis is the most commonly used illicit drug among youth and young adults in both developed and developing countries (1). It is estimated that 124-203 million people use cannabis worldwide (2) with a prevalence peaked between 20-24 years of age. Cannabis dependence caused 2 million years lived with disability in 2010 (1).

There is still greater uncertainty surrounding the estimates of cannabis use than of other drugs, such as cocaine or opioids, which is attributable to the scarcity of credible estimates of the prevalence of cannabis use in many countries (2). In some countries cannabis dependence produces more years lived with disability than drugs like amphetamines and cocaine, largely because the rate of cannabis use is higher than those of the stimulant drugs (1). Countries with the highest rate of burden of cannabis dependence are United States, Spain, France, and Australia (2, 3).

In relation to cannabis use in Sweden, it is reported that in 1971, 16 % of girls and 14 % of boys in the 9th grade of compulsory school reported that they have used cannabis at least once. Only few years later, however, this percentage had dropped by more than half but in the 1990s, however, the incidence of cannabis use rose once more, with percentage of 9th grade pupils who had used drugs at some point peaking in 2001 and 2010 (4). This might be interpreted as a general symptom of more liberal and individualistic attitudes towards cannabis and other drugs (5). In general, the level of use has been lower than in several other European countries and the USA (6-8).

The life-time risk of dependence in cannabis users has been estimated at about 9%, but rises to one in six among those who initiate use in adolescence (9). Consumption generally declines with age (10). However, about 10% of people who ever use cannabis, and one-third to half of those who use it daily, will become dependent on cannabis, and will use it despite having problems associated with its use (11).

The main reason why most young people use cannabis is to experience a so-called high: mild euphoria, relaxation, and perceptual alterations, including time distortion and intensification of ordinary experiences such as eating, watching films, listening to music, and engaging in sex (9, 12).

Cannabis is a generic term for preparations derived from the cannabis sativa plant (marijuana, hashish, and hash oil). The cannabis plant contains more than 60 unique cannabinoids. The one that is primarily responsible for the psychoactive effects is delta-9-tetrahydrocannabinol (THC). THC gives rise to transitory psychotic symptoms and impaired cognition in healthy volunteers; and, in people with a genetic risk of psychosis, an exaggerated psychotic response has been observed (13, 14)

In the human brain, the effects of the main psychoactive component of cannabis (THC) are mediated via cannabinoid CB1 (cannabinoid receptor type 1) receptors. CB1 receptors are one of the most common groups of receptors in the brain, and are widely distributed in the regions involved in cognition, memory, reward, pain perception, and motor coordination. They are found in basal ganglia, amygdala, the hippocampus, the cingulate cortex, and the molecular layer of the cerebellum. CB1 is generally known to suppress excitatory or inhibitory synaptic transmission. CB1 receptors are situated on presynaptic terminals that release neurotransmitters, such as glutamate and gamma-aminobutyric acid (GABA) (9, 14-16).

A shift in available cannabis preparations from resinous "hash" to intensively grown high potency herbal preparations, often referred to as skunk, took place in the late 1990s in developed countries, and the adverse health effects of these highly potent preparations are still unclear (17, 18).

Not only the detrimental effects of high potent preparations of cannabis but also the long-term adverse effects of cannabis are not well known. A systematic review by Calabria et al (19) did not find sufficient evidence to determine an increased mortality among cannabis users compared to no users. They concluded that there is a need for long-term cohort studies that follow individuals into old age, when the probability of detrimental effects of cannabis use are more likely to emerge such as cancer, pulmonary diseases and coronary heart disease.

What is known is that cannabis use is highly correlated with use of alcohol, tobacco, and other illicit drugs, all of which adversely affect health. Those at highest risk of cannabis dependence have a history of poor academic achievement, deviant behaviour in childhood and adolescence, rebelliousness, and poor parental relationships (9). There is also an extensive literature on the association between cannabis and mental health outcomes, but with important knowledge gaps that will be explored in this thesis

1.2 Psychosis

Psychosis means a mental state involving loss of contact with reality with presence of delusions and/or hallucinations. It may include disordered thought or speech, behavioural disorganization, gross excitement and over activity (20).

Psychosis exists in the general population as a continuous phenotype rather than as an all-or-none phenomenon (21). Psychosis is not exclusive of schizophrenia and occurs in various diagnostic categories of other disorders including other non-affective psychoses and affective disorders such as bipolar and major depressive disorders.

The criteria used to distinguish between these different categories of psychotic disorders are based on duration, dysfunction, associated substance use, and presence of depression or mania (22).

Many people with diagnoses of other psychoses including non-affective and affective psychoses are later diagnosed with either schizophrenia or affective disorders e.g. bipolar disorder (23-25). Conversely, a number of patients with severe depression have psychotic features (26).

1.2.1 Non-affective psychoses

Schizophrenia

Schizophrenia is a leading cause of disability worldwide (27) with the highest proportion occurring in men during young adulthood. The rate ratio for males:females is 1.4:1 (28). Lifetime prevalence has been reported in the range of 0.5% to 1.6% (29).

Schizophrenia is a rare and severe disabling disorder of unknown clear aetiology (30). Multiply risk factors including obstetric complications, some immigrant ethnic groups, urban life, advanced paternal age, positive family history, and cannabis use (22, 31) have been associated with an increased risk of developing schizophrenia.

In most cases, schizophrenia is preceded by a prodromal phase that can be manifested as non-specific clinical states, with depressive and anxiety symptoms (32), which can last up to several years (33, 34). These prodromal symptoms are non-specific of schizophrenia, and most people with these symptoms will not develop schizophrenia.

The onset of Schizophrenia typically occurs between the late teens and the mid-30s, with onset prior to adolescence rare, and infrequently after the age of 45 years. Psychotic symptoms tend to be episodic over time, with their emergence or worsening associated with a potential risk to self or others, often requiring temporary hospitalization (35). Negative symptoms and cognitive problems tend to be more stable over time, and contribute significantly to functional impairment debilitating and deteriorating disorder with poor outcome (22).

Hallucinations and delusion have been consistently given as a diagnostic criteria for schizophrenia throughout the history of the Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Diseases (ICD). According to DSM V and ICD-11, Schizophrenia Spectrum and Other Primary Psychotic Disorders are defined by abnormalities in one or more of the following five domains: delusions, hallucinations, disorganized thinking (speech), grossly disorganized or abnormal motor behaviour (including catatonia), and negative symptoms, which occur with sufficient frequency and intensity to deviate from expected cultural or subcultural norms.

The multiplicity of the clinical presentations of schizophrenia and the fact that its outcomes can range from full recovery to profound disability have confronted its credibility as a single disorder and more as heterogeneous disorder. As a result, there have been many attempts to define subtypes of schizophrenia which have a more uniform clinical picture which might show meaningful differences in prognosis, and facilitate identification of etiological factors of subtypes of schizophrenia (36).

Prognosis is poor outcome in less than 50% of patients and, similarly, with good outcome in less than 50% of patients. Therefore, the course and outcome of schizophrenia is characterised by mainly unexplained heterogeneity rather than uniform poor outcome (37). Even in patients with good control of positive symptoms, return to function could remain a challenge. Few patients currently resume employment, and about a third, remain with a severe symptomatology (22).

In the past 20 years, new agents, known as the second generation antipsychotics (clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole) have been introduced for treatment. Although the new second-generation antipsychotic drugs are effective in treating positive symptoms with a reduced burden of motor side-effects, the promise of efficacy against negative and cognitive symptoms has not been borne out (38). Additionally, the new antipsychotics tend to induce a high incidence of metabolic side-effects (22).

People with schizophrenia are at increased risk for premature death associated with comorbid somatic conditions (39) and high suicide rates (40, 41). Overall, People with schizophrenia have twice as high mortality rate compared with the general population (40-42). Several studies have suggested this mortality gap is unchanging and even widened over time after the inclusion of second generation antipsychotics (40, 41, 43). It is sobering to reflect whether risk factors such as cannabis use could be an explanatory factor for this mortality gap.

Other non-affective psychoses

Other non-affective psychoses such as brief psychosis are characterized by acute onset of psychotic symptoms that emerge without a prodrome and reach their maximal severity within weeks in individuals, in most of the cases the individuals have no history of another psychotic disorder. Symptoms may include delusions, hallucinations, disorganization of thought processes, perplexity or confusion, and disturbances of affect and mood. The duration of the episode rarely exceeds three months.

Approximately 80% of developmental psychotic experiences are transitory and disappear over time. There is evidence, however, that transitory developmental expression of psychosis may become abnormally persistent and subsequently cause clinical impairment, depending on the degree of environmental risk the person is additionally exposed to (44).

1.3 Depression

One other important but much less often explored field of research is depression with psychotic features. Major depression with psychotic features is associated with greater illness severity compared with nonpsychotic major depression, as well as poorer prognosis, increased mortality, and distinct patterns of response to standard treatments for depression (45-47).

While depressive symptoms are well recognized as forming part of the prodrome of schizophrenia, the presence of psychotic-like experiences in depression is less well understood (48).

The evidence that cannabis use increases the risk of psychotic symptoms implies that there may also be associations between cannabis and affective disorders with psychotic features, such as schizoaffective and bipolar disorders.

1.3.1 Affective psychoses

Opinions differ about whether schizophrenia and affective disorders, specially bipolar disorder, are the clinical outcomes of entirely different processes, or whether these two disorders have more identical processes (25) having a common environmental cause or a shared causative risk factor is responsible for part of each disorder. Epidemiological and genetic molecular studies have found evidence that schizophrenia and bipolar disorder share some common genetic causes [12,13]. An intermediate phenotype is schizoaffective disorder, which shares diagnostic features of both disorders (49, 50). Knowledge of the common causes of these disorders might be beneficial for research and clinical propose. There may also be other risk factors in common across these disorders, such as cannabis use.

1.4 Cannabis and Psychosis

Cannabis is well known for psychogenic effect on the brain. Its ability to induce paranoia and acute psychotic reactions was noted as early as 1845 by the French psychiatrist Moreau de Tours (14). In 1987, the Swedish conscription cohort 1969/70 was used for the first time to examine the association between cannabis and schizophrenia (51). This study was later refined by Zammit et al (2002) again showing an association between cannabis and schizophrenia (52), findings on the association between cannabis and schizophrenia spectrum disorders were replicated in other longitudinal studies in the Netherlands (53), Germany (54) and New Zealand (55, 56), as summarized in a systematic review by Moore et al (57).

All these studies support the concept of temporality by showing that cannabis use preceded the diagnoses of psychosis which support a causal relationship. Further evidence for causal association is provided by the presence of a dose-response relationship between cannabis and schizophrenia (58). In addition, the association persisted after controlling for many potential confounding factors such as disturbed behaviour, low IQ, place of upbringing, cigarette smoking, poor social integration, gender, age, ethic group, level of education, unemployment, single marital status and previous psychotic symptoms (58). On the other hand residual confounding by for example prodromal symptoms or personality traits associated with both cannabis use and an increased vulnerability for psychoses cannot be ruled out. The ongoing concern, about whether the association is causal or not, is still of great importance for public health as well as scientific (59, 60).

The substantial variation in the incidence across places and minority groups, suggests that environmental factors such as cannabis use may have an important role (13). However, it has been demonstrated that the incidence rates of schizophrenia are rather decreasing than increasing whereas the cannabis use is increasing for example in UK (8). However, as there are many different risk factors operating at the same time (e.g. migration, advanced parental age, social adversity, and perinatal complications) and comparable incidence estimates are difficult to obtain, it is difficult to draw any conclusions.

1.4.1 Possible explanations of the observed association

One hypothesis postulating the strongest form of causal link is that heavy cannabis use cause a psychosis that would not otherwise have occurred (61, 62). A second hypothesis is the "Stress-vulnerability model of etiological" which assumes that genetic factors operate by making individuals selectively vulnerable for environmental risk. The neurodevelopmental model of schizophrenia (63), which posits that the illness is the end state of abnormal neurodevelopmental process that started years before the illness onset, supports the endocannabinoid hypothesis of schizophrenia. Endocannabinoid signalling is present during gestation, and early infancy and plays a critical role in neuronal proliferation, migration,

axonal guidance, positioning of cortical interneurons, and synaptogenesis, the neurodevelopmental role of this system continues during adolescence when regions such as hippocampus and prefrontal cortex are still undergoing marked development (64-66).

It has been hypothesized that repeated exposure to cannabis during adolescence and young adulthood may cause permanent dysregulation of the dopaminergic and GABA system development (67) and impaired neural connectivity (68).

Most of the work on neurobiology of psychotic syndrome to date has focused on alterations in glutamate, dopamine and GABAergic system.

The effects of the main psychoactive component of cannabis (THC) are mediated via cannabinoid CB1 receptors (15, 16). THC may increases dopamine release, although THC may not induce a significant increase dopamine in healthy volunteers, it does so in patients with schizophrenia and their relatives, implying that a genetic vulnerability to react in an exaggerated manner to cannabis (69-71). Animal experiment has showed that CB1 receptor stimulation impairs GABA functioning (72), and it has been also showed that exogenous cannabinoids such as THC can also lead to decreased GABA release (73, 74).

Given that dopaminergic functioning is intertwined with, and regulated by, GABAergic, glutamatergic and endocannabinoid signalling, and that CB1 receptor activation enhances mixed synaptic transmission among these neurotransmitters (75), it is hypothesized that THC may induce psychotic syndrome through different pathways.

1.4.2 Remaining questions and implications for research

While evidence has grown stronger in recent years that use of cannabis in adolescence is associated with later risk of schizophrenia (57), several issues need to be clarified regarding this association. It is of clinical as well as public health importance to study whether the increased risk of schizophrenia varies over time, course of disease and mortality among schizophrenic patients with a history of cannabis use compared with those without, and whether cannabis use is also associated with other psychiatric disorders such as brief psychosis, depression, and risk of death.

While it is also hypothesized that the adverse effects of cannabis use are most pronounced among adolescents and decline with increasing age, the long-term impact of cannabis use during adulthood and how the increased risk of schizophrenia associated with cannabis use varies over time is not known (11).The cumulative evidence suggests that earlier initiation of cannabis use increases the chance of becoming a daily or nearly daily user of cannabis (76, 77) and this, in turn, increases the risk of becoming dependent on cannabis and use it despite experiencing problems (11, 76).

The inclusion of cannabis-induced psychotic disorder in the ICD-10 and DSM-IV has also reinforced the idea of the importance of studying the association between cannabis use and

other affective and non-affective psychoses. Other psychoses such brief psychosis and cannabis-induced psychosis could be an early sign of schizophrenia rather than a distinct clinical entity (78). Views differ about whether an environmental factor such as cannabis use can be a common causative risk factor for schizophrenia, brief psychosis, and depression, or whether cannabis use is only associated with schizophrenia (25). Since the Swedish conscription cohort has power to assess the specific outcome schizophrenia, it is of scientific as well as clinical interest to find out to what extent cannabis is a risk factor for schizophrenia in particular, or if the association with cannabis use can be found for also other psychiatric disorders.

In recent years, concerns have been raised by increasing rates of cannabis use and depression among young people in many countries. These have been paralleled by an increasing concern about suicide among young adults for which problematic drug use and depression are both risk factors (79). To date, two systematic reviews (57, 79) and one meta-analysis have (80) investigated the association between cannabis use and the development of depression. They found that longitudinal studies provided mixed evidence on the nature of the association between cannabis use and depression and that even though heavy cannabis use may increase depressive symptoms; this relationship may be explained by confounding factors. They concluded that more longitudinal studies, particularly taking into account significant confounding factors, are needed. An earlier study from the conscript cohort did not find an increased risk of suicide among cannabis users (81). Given the strong association between severe depression and suicide, the association between cannabis and depression needs to be clarified.

Several studies have addressed the effect of cannabis on the course of illness in patients with schizophrenia. Zammit et al. (82) reviewed longitudinal studies of people with psychosis and found that cannabis use was consistently associated with increased relapse or rehospitalisation, and poorer adherence to treatment. They noted, however, that many studies had limitations, such as lack of control for baseline severity, and confounding. In order to overcome methodological limitations, Foti et al. (83) followed 229 patients with schizophrenia for 10 years with the aim of examining the association between cannabis use and course of illness. They concluded that cannabis is associated with an adverse course of psychotic symptoms in schizophrenia, but that the association was bidirectional, i.e. psychotic symptoms also increased cannabis use. Thus, while there is substantial evidence on the role of cannabis in persons with established psychoses, it would be of clinical importance to know whether the course and outcome of schizophrenia differ in people with a history of cannabis use prior to the onset of schizophrenia compared with those without.

Subjects with psychotic disorders including schizophrenia have two to three times higher mortality rates than those in the general population (40-42). With respect to cause of death, about 40% is explained by suicide and other unnatural causes, and approximately 60% of premature deaths are from natural causes as cardiovascular and pulmonary disease (40, 42). Several studies have suggested this mortality gap is unchanging and even widened over time

after the inclusion of second generation antipsychotics (40, 41, 43). The fact that cannabis use increases risk of psychosis in a dose-response fashion and that patients with psychosis who continue to use cannabis show more severe and persistent symptoms suggests that cannabis use might increase the risk of death among psychotic patients. Thus, it is still not known whether or not cannabis use does increase mortality in general. Also, it is important to find out whether or not previous cannabis use increases the already high mortality among psychotic patients.

2 Aim and Research questions

2.1 Aim

The overall aim of this thesis was to investigate the association between cannabis use and psychiatric disorders with emphasis on schizophrenia, other psychoses, depression and long term effects on mortality.

2.2 Research questions

1. Is there at long-term follow up an increased risk of schizophrenia and other psychoses among cannabis users compared with non-users?

2. Is there an increased risk of depression among cannabis users compared with non-users?

3. Do schizophrenia patients with a cannabis history have another prognosis, with regard to readmission and hospital duration, compared to those without a cannabis history?

4. Is there a difference in mortality between psychotic patients with a history of cannabis use and those without a history of cannabis use?

5. Is there a difference in mortality between Swedish conscripts with a history of cannabis use and those without a history of cannabis use?

3 Methods

Table 1. Overview of the studies

STUDY	I	II	III	IV
Research Question	Is there at long-term follow up an increased risk of schizophrenia and other psychoses among cannabis users compared with non-users?	Is there an increased risk of depression among cannabis users compared with non-users?	Do schizophrenia patients with a cannabis history have another prognosis compared to those without a cannabis history?	What is the risk of death among the conscripts and psychotic patients? comparing cannabis users with non-users of cannabis
Data source	Swedish conscription cohort 1969/70			
Study design	Cohort study	Cohort study	Cohort study	Cohort study
Follow-up period	1973-2007	1973-2007	1973-2007	1969-2011
Population	41 943 conscripts	45 087 conscripts	357 subjects with a diagnosis of schizophrenia during the follow-up period among 45 375 conscripts	45 375 conscripts 683 subjects with psychotic disorders
Exposure variable	Cannabis use at conscription			
Outcome variable	First diagnosis of schizophrenia and brief psychosis throughout the follow-up period (four decades)	First diagnosis of depression (unipolar, bipolar disorder and affective psychosis) , and schizoaffective disorder	Prognosis of schizophrenia, with regards to readmission and hospital duration	Overall risk of death among the conscripts, and risk of death among persons with psychotic disorders
Covariates	Psychiatric diagnosis at conscription, IQ score, disturbed behaviour, smoking, brought up in a city	Prior personality disorders at conscription, IQ, disturbed behaviour in childhood, social adjustment, risky use of alcohol, smoking, early adulthood socioeconomic position, use of other drugs, brought up in a city	Diagnosis of personality disorders at baseline, family socio-economic position, IQ score, civil status during follow-up, place of residence at conscription, risky use of alcohol at conscription, and use of other drugs.	Contact with juvenile authorities, run away from home, truancy, smoking, solvents abuse, risky use of alcohol, psychiatric diagnosis, parents divorced, use of other drugs, use of intravenous drugs, and IQ score.
Measures	Odds ratio for first diagnosis of psychotic disorders	Hazard ratio for first diagnosis of depression , and schizoaffective	Median, Odds ratio, and Rate ratio for readmission and hospital duration	Hazard ratio of death in relation to cannabis use at conscription
Analysis	Logistic Regression	Cox proportional hazard modelling	Multinomial Logistic and Negative binomial Regression	Cox proportional hazard modelling

3.1 Study population and data

3.1.1 Study population

For the studies in this thesis, we linked the Swedish conscription cohort 1969/70 to other Swedish registers. In studies I, II and III, the Swedish conscription cohort 1969/70 was followed until 2007. For Study IV, we used versions of the inpatient register and other socio-demographic databases updated until 2011.

Of all 50 087 Swedish conscripts in 1969/70, over 93% were aged 18–19 years. Only 2–3% of men were exempted from conscription, mainly because of a severe mental or physical handicap or a congenital disorder. Around 10% of subjects had missing information on cannabis use. A total of 3 918 (8.6%) individuals died during the 42 years of follow-up.

Conscription examination was compulsory for all young Swedish men until recently. However, the Swedish conscription cohort 1969/70 is the only one that has retained personal identification on matters related to drug use and other behavioral characteristics, thereby enabling record linkage with the Total Population Register, Population and Housing Censuses, the Inpatient Register, and the Swedish Cause of Death Register.

3.1.2 Data bases used

Swedish conscription cohort 1969/70

The data used in this thesis were derived from the Swedish conscription cohort 1969/70, based on a nationwide survey of 50 087 Swedish men who were examined for compulsory military training during autumn 1969 to spring 1970.

The conscription tests normally took place during the last year of high school (ages: 18-19 years) and were completed during two days. The tests included a medical examination, various physical tests, cognitive tests, and two non-anonymous, self-report questionnaires. One was related to psychosomatic and social circumstances in childhood and adolescence, the other to substance use: narcotic drugs, alcohol, sniffing of solvents, and tobacco smoking. The conscripts were informed that participation in the questionnaires was independent of the rest of the examination, and would not affect selection or ranking (84).

All conscripts undertook a structured interview by a psychologist, and were also screened for psychiatric symptoms. Those presenting psychiatric symptoms were referred to a psychiatrist, and any diagnosis was recorded according to the Swedish version of the International Classification of Diseases, 8th revision.

Total Population Register

Since 1968, Statistics Sweden holds a register of the total population based on information from the tax administration. The register includes data on immigration and emigration.

Population and Housing Censuses

Between 1960 and 1990 a compulsory population and housing census was performed every five years. The resulting register contains information about both individuals (occupation, education, civil status) and households (regarding number of individuals in each household).

Inpatient Register

The Swedish National Inpatient Register, which records all inpatient admissions to hospitals in Sweden, was used to identify hospital admissions since 1970. The Swedish register recorded approximately 83% of all psychiatric admissions in 1973, 97% in 1974–1983, and 95% in 1984–1986, and has been virtually complete since 1987.

Swedish Cause of Death Register

The Swedish Cause of Death Register covers all deaths of residents of Sweden since 1961. The causes of death were recorded according to the International Classification of Diseases (ICD). ICD-8 was used from 1969, ICD-9 from 1987, and ICD-10 from 1997.

3.2 Exposure

Information on cannabis use was obtained from the surveys at the time of conscription. Questions were asked whether the subjects had ever used drugs, which drugs they had ever used, the first drug used, the drug most commonly used, frequency of use, and the use of specific drugs taken from a pre-prepared list.

Level of cannabis use was determined through a question on the number of occasions the subject had used cannabis: Never, Once, 2–4, 5–10, 11–50, >50. We compared outcomes for subjects having ever used cannabis (thereby including everyone who reported cannabis use in any of the use categories) with those who had never used cannabis, and also compared outcomes for those reporting the highest level of use (>50 times) with those who had never used cannabis.

3.3 Outcomes

1. **Long-term risk of schizophrenia and other psychoses including brief psychosis (STUDY I)**
   The primary outcomes of interest were first diagnosis of schizophrenia as well as other non-affective psychoses including brief psychosis throughout the follow-up period.

2. **Risk of depression including unipolar depression, bipolar disorder and affective psychosis (STUDY II)**
   The primary outcome of interest was first diagnosis of depression (unipolar depression, bipolar disorder and affective psychosis).

3. **Prognosis of schizophrenia, with regard to readmission and hospital duration (STUDY III)**
   We assessed the duration of first admission, total number of hospital days, and number of readmissions among patients with a diagnosis of schizophrenia.

4. **Risk of death among people with a psychotic disorder (STUDY IV)**
   The primary outcome was mortality in subjects with psychotic disorder.

5. **Overall risk of death in the Swedish conscription cohort (STUDY IV)**
   The primary outcome was mortality in the total cohort.

3.4 Covariates

We selected potential confounding variables on the basis of prior research indicating that they are likely to be associated with both cannabis use and the different outcomes (52, 57, 79, 80, 82, 85, 86).

Contact with juvenile authorities

Subjects were asked whether they had been in contact with the juvenile authorities: several times, sometimes, never.

Run away from home

Questionnaire information was available on whether the subjects had run away from home during childhood: two or more times, once, never.

Truancy

Data on truancy were based on self-reported information: once a week, once a month, once per term, occasionally.

Smoking

Smoking was based on questionnaire information, and categorized as: >20 cigarettes/day, 11-20 cigarettes/day, 6-10 cigarettes/day, 1-5 cigarettes/day, non-smoking.

Solvent abuse

Solvents abuse was obtained from the questionnaire, and categorized as : >10 times, 2 to 10 times, once, never.

Risky use of alcohol

Risky use of alcohol was derived from questions on high consumption of alcohol: none versus at least one of the following indicators – consumption of at least 250g 100% alcohol/week; have taken an eye-opener during a hangover; have been apprehended for drunkenness; have reported being drunk often.

Psychiatric diagnosis at conscription

Psychiatric diagnosis at conscription was assessed by a psychiatrist, and categorized in this study as: any versus none.

Parents divorced

Data on whether subjects had grown up with divorced parents was obtained from the questionnaire: yes or no.

Use of other drugs at conscription

Information on use of other drugs was obtained from the questionnaire. The following types of drugs were specified: preludin, amphetamine, lysergic acid diethylamide, morphine, mebumal, and opium. Use of other drugs was categorized as ever used versus never used

Use of intravenous drugs

Intravenous drug use was based on self-reported information from the questionnaires, and categorized as: several times, once, never.

IQ score

IQ score was obtained at time of conscription and based on four main subtests: verbal IQ, visuospatial ability, general knowledge, and mechanical ability. Results on the four subtests were aggregated to give an overall standardized intelligence score, ranging from 1 to 9 (< 74, 74 to 81, 82 to 89, 90 to 95, 96 to 104, 105 to 110, 111 to 118, 119 to 126, > 126).

Brought up in a city

"Brought up in a city" was based on self-reported information on upbringing: any one of Sweden's three large metropolitan areas (Stockholm, Gothenburg, Malmö) versus other areas.

Family socio-economic position

Information on family socio-economic position was based on Census 1960 on data on each conscript's father's occupation: non-manual (collapsed intermediate and high non-manual), low non-manual, manual (unskilled, skilled) and others (farmers, self-employed, unclassified).

Early adulthood socioeconomic position

"Early adulthood socioeconomic position (Early adulthood SEP)" was based on information from Statistics Sweden on occupation: 1) high/intermediate non-manual 2) low non-manual 3) manual skill/unskilled 4) farmers/self-employed/ unclassified.

Civil status during the follow-up

Information on civil status was based on Census 1970, 1975, 1980, 1985 and 1990. We categorized as a dichotomous variable ever married versus never married.

3.5 Statistical analyses

Cox proportional hazards modeling

Cox proportional hazard modelling was used to assess the relative risk of developing depression in relation to cannabis use at conscription (Study II), and also the relative risk of death in relation to cannabis use at conscription (Study IV). We assessed the proportional hazard assumption between cannabis use and each outcome by using a Kaplan-Meier plot. Log-rank tests were used to test equality across strata. We tested the equality-across-strata of each individual confounder to explore whether or not to include it in the final model. The quality of each model was tested by running a logistic regression and applying Hosmer-Lemeshow's GOF test.

Negative binomial regression

Negative binomial regression was used in Study III to estimate rate ratios with 95% confidence intervals (CIs) for duration of first admission, total number of hospital days, and number of readmissions among subjects who had ever used cannabis compared with those who had never used cannabis. This method models count variables rather than dichotomous outcomes. Negative binomial regression was used instead of Poisson regression because of over-dispersion of variance relative to the mean during follow-up (87).

Logistic and multinomial logistic regression

Logistic regression was used to calculate odds ratios and 95% confidence intervals (CIs) for developing schizophrenia, brief psychosis and other non-affective psychoses among cannabis users, and to assess the risk of schizophrenia and brief psychosis by decade, from 1970 until 2007 (Study I). Logistic regression refers specifically to a regression where the dependent variable is binary; in the case of more than two categories of the dependent variable, the regression is referred to as a multinomial logistic regression (Study III).

Fisher's exact test

Differences in first pre-morbid psychiatric diagnosis of schizophrenia and type of schizophrenia at first admission were tested using Fisher's exact test (Study III). Fisher's exact test is used when the intention is to conduct a chi-square test, but one or more cells in the contingency table have an expected frequency of five or less.

3.6 Ethical approval

The data were treated according to recommendations of the Swedish Data Inspection Board. Permission to use the conscription database for research purposes and to perform the relevant record linkages was granted by the Stockholm Regional Ethical Review Board (dnr 121/84, dnr 10/86, dnr 188/91, dnr 2010/5:2).

4 Results

4.1 Risk over time of schizophrenia and brief psychosis (Study I)

People with the highest level of cannabis use showed an approximately four-fold increase in the odds of schizophrenia, and a two-fold increase in the odds of brief psychosis and other non-affective psychoses, compared with non-users. A dose-dependent association was found between frequency of cannabis use and risk of schizophrenia (p for trend <0.01). The dose–response association was weaker for brief psychosis and other non-affective psychoses, although the p value for trend was significant in the case of brief psychosis

As shown in Table 2, heavy cannabis users retained a higher risk of schizophrenia throughout the follow-up period compared with non-users. The odds ratios for brief psychosis did not decline over the decades, but appeared actually to increase over time, particularly among people with the highest use, although this was based on a small number of cases and the CIs were wide.

Table 2: Adjusted odds ratios for schizophrenia by decade of first admission. The category "Ever used cannabis" comprises all who reported cannabis use, including those who reported "> 50 times".

	1970-1979	**1980-1989**	**1990-1999**	**2000-2007**
	OR Adjusted*	**OR Adjusted***	**OR Adjusted***	**OR Adjusted***
Never used cannabis	1	1	1	1
Ever used cannabis	2.2 (1.4-3.3)	1.9 (1.1-3.5)	1.2 (0.5-2.8)	0.7 (0.2-3.0)
>50 times	4.1 (2.2-7.6)	3.9 (1.6-9.4)	2.5 (0.7-9.0)	2.7 (0.5-14.0)

* Diagnosis of psychiatric illness on conscription, disturbed behaviour, low IQ score, brought up in city, cigarette smoking.

4.2 Risk of depression (unipolar depression, bipolar disorder and affective psychosis) (Study II)

Table 3 shows hazard ratios for depression (any case of unipolar disorder, bipolar disorder and affective psychosis) by level of reported cannabis use. Only subjects with the highest level of cannabis use showed an increased crude hazard ratio for depression, but this association disappeared after adjustment for the confounders.

Heaviest cannabis use (>50 times) was associated with an increased risk of unipolar depression (HR 1.8, 95% CI, 1.2-2.7), but this association was eliminated after adjustment for confounding. Disturbed behaviour in childhood was the confounder that most attenuated the hazard ratios.

Table 3: Hazard ratios for overall depression (any case of unipolar disorder, bipolar disorder and affective psychosis) by reported frequency of cannabis use

Cannabis use	No. exposed	No. cases	HR Crude	HR adjusted*
Never	39 978	990	1	1
Once	1 202	28	0.9 (0.6-1.4)	0.9 (0.6-1.5)
2–4	1 486	51	1.4 (1.1-1.9)	1.2 (0.8-1.8)
5–10	839	24	1.2 (0.7-1.8)	1.1 (0.6-1.8)
11–50	727	24	1.3 (0.8-1.9)	0.6 (0.3-1.2)
>50	855	29	1.5 (1.0-2.2)	0.8 (0.4-1.5)
TOTAL	45 087	1 146		

* Prior personality disorders at conscription, IQ, disturbed behaviour in childhood, poor social adjustment, risky use of alcohol, smoking, early adulthood socioeconomic position, use of other drugs, brought up in a city.

4.3 Prognosis of schizophrenia, with regard to readmission and hospital duration (Study III)

Schizophrenia patients with a history of cannabis use showed a higher median duration of first hospital episode than those without (59 days v. 30 days). Patients with a history of cannabis use also had a higher median rate of readmission (10 times v. 4 times). Also, the total number of hospital days was higher in patients with a history of cannabis use compared with those without (547 days v. 184 days).

Table 4 shows the distribution of numbers of hospital days after controlling for confounding factors. There was more than a two-fold increase in the odds of a hospital stay lasting more than 2 years (>730 days) in people who had used cannabis compared with those without cannabis use after controlling for confounding (adjusted OR= 2.4, 95% CI 1.1–7.4).

Table 4. Odds ratio for total number of hospital days among schizophrenia patients

	< 45 days	**46 to 179 days**	**180 to 729 days**	**>730 days**
Never used cannabis	71 (27%)	63 (24%)	71 (27%)	56 (21%)
Ever used cannabis	11 (19%)	12 (21%)	13 (22%)	22 (38%)
Adjusted OR (95% CI)*	1	1.6 (0.6-4.2)	1.3 (0.5-3.7)	2.4 (1.1-7.4)

Table 5 shows the distribution of numbers of readmissions after controlling for confounding factors. There was an almost four-fold increase in the odds of having more than 20 hospital readmissions in patients with a history of cannabis use compared with non-users. This was slightly reduced after adjustment for confounding (adjusted OR 3.1, 95% CI 1.3–7.3).

Table 5. Odds ratio for number of re-admissions among schizophrenia patients

	< 4 times	**5 to 20 times**	**>20 times**
Never used cannabis	138 (53%)	96 (37%)	27 (10%)
Ever used cannabis	25 (43%)	16 (28%)	17 (29%)
Adjusted OR (95% CI)*	1	0.8 (0.4-1.7)	3.1 (1.3-7.3)

* Table 4 and 5 are adjusted for diagnosis of personality disorders at baseline, family socioeconomic position, IQ score at conscription, civil status during follow-up, place of residence at conscription, risky use of alcohol at conscription, and use of other drugs at conscription

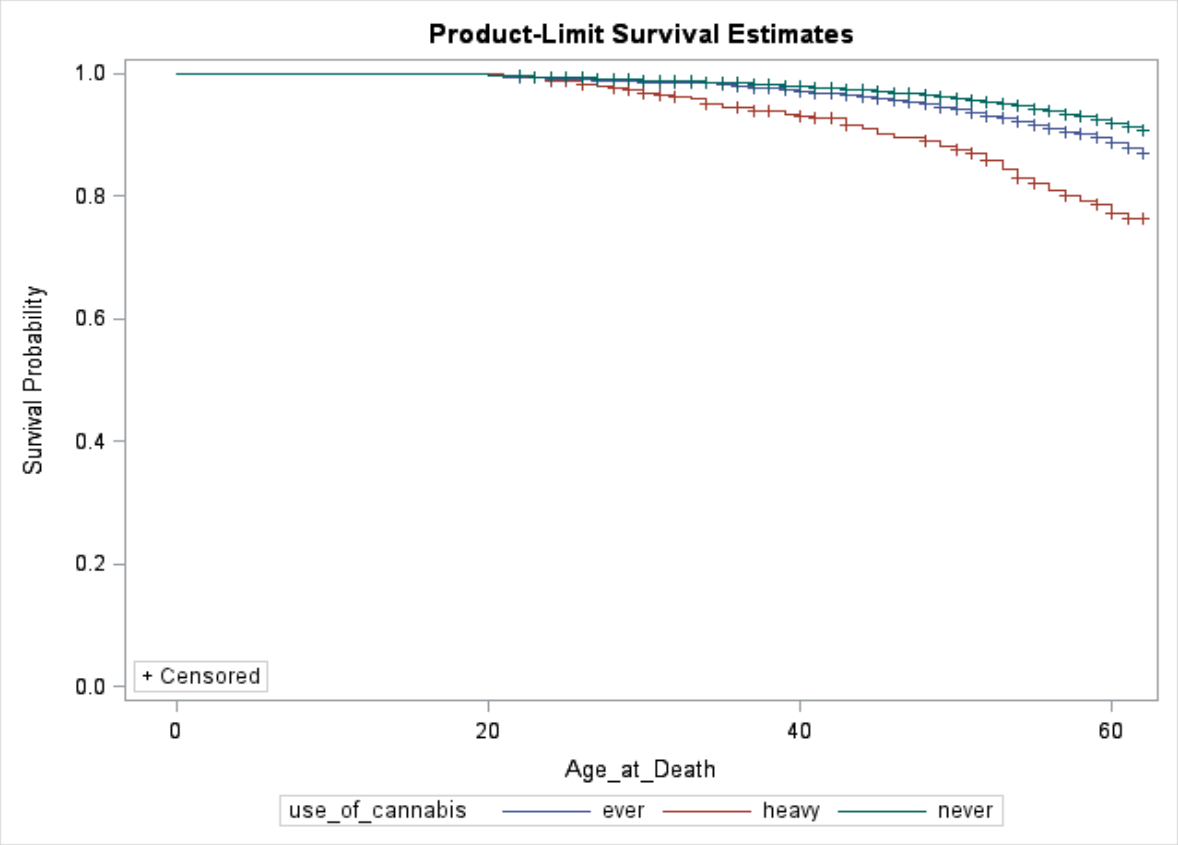
4.4 Risk of death among people with psychotic disorders (Study IV)

Subjects with a diagnosis of psychotic disorder had an increased risk of death compared with those without a diagnosis of psychotic disorder. We did not find that excess mortality was higher among subjects with a history of cannabis use (ever users: 3.8, 95% CI 2.8-5.0; heavy users: 3.8, 95% CI 2.6-6.2) compared with never users of cannabis (3.7, 95% CI 3.1-44).

4.5 Overall risk of death in the Swedish conscription cohort (Study IV)

Figure 1 shows the survival curve by age at death according to cannabis use/non-use (never users, ever users, and heavy users). Ever users as well as heavy users had an earlier age at death compared with non-users. The difference was statistically significant for both categories of users versus never users (Log-Rank test<0.001). All subjects reporting cannabis use had an increased hazard ratio for mortality. After adjustment for confounders, the association persisted only for heavy users (1.4, 95% CI 1.1-1.8)

Figure 1. Survival curve by age at death according to cannabis use: never users vs. ever users and heavy users



5 Discussion

This thesis aimed to contribute to a better understanding of the association between cannabis use and psychiatric disorders with emphasis on schizophrenia, other psychoses, depression and long term effects on mortality.

Is there at long-term follow up an increased risk of schizophrenia and other psychoses among cannabis users compared with non-users?

The thesis confirms the strong associations between cannabis and psychotic disorders, with a more than three-fold increased risk of schizophrenia, and two-fold increased risk of other psychotic outcomes in the most frequent cannabis users. It seems as if the association between cannabis and schizophrenia may be stronger than that between cannabis and other non-affective psychoses.

We observed that heavy cannabis users retained a higher risk of schizophrenia throughout the follow-up period compared with non-users. This may indicate that heavy users continue using cannabis for a longer period. Heavy cannabis use during adolescence may also trigger persistent psychosis according to the 'cannabis–psychosis persistence model' presented by Kuepper et al. (88), The model postulates that cannabis, particularly, has an effect on persistent types of psychoses, such as schizophrenia, in a dose-response fashion.

Is there an increased risk of depression among cannabis users compared with non-users?

Our main finding was that, after control for confounders, especially markers of disturbed behaviour during childhood, there was no increased risk of severe depression among cannabis users at ages 18 to 20. However, the finding of a substantially increased risk of schizoaffective disorder among cannabis users is consistent with previous findings on the associations between cannabis and different schizophrenia-related disorders (57).

Our results indicate that the association between cannabis use and subsequent severe depression is likely to be confounded by risk factors common to both, such as disturbed behaviour during childhood. Cannabis use is a biologically plausible contributory cause of schizophrenia. An association has also been found, albeit less consistently, between cannabis use and severe depression (57, 79, 80). More research is needed to explore whether there is any association between cannabis use and milder forms of depression.

Do schizophrenia patients with a cannabis history have another prognosis, with regard to readmission and hospital duration, compared to those without a cannabis history?

Schizophrenia patients with a history of cannabis use faced a significantly higher burden of inpatient care, with regard to hospital readmission and hospital duration, compared with those without a history of cannabis use.

There are a number of possible mechanisms that might explain the associations between cannabis use and increased relapses and poorer clinical outcomes in schizophrenia. It has been suggested that cannabis use can cause long-lasting dysregulation of the endogenous anandamide/cannabinoid system that mediates the effect of tetrahydrocannabinol within the brain (53). It has also been suggested that cannabis increases the number of cannabinoid receptors in the brain, causing increased vulnerability to repeated psychotic episodes (89). Cannabis use has also been found to correlate with poor compliance with medication in first-episode schizophrenia (90-92). All of these factors may result in poorer outcomes.

Is there a difference in mortality between psychotic patients with a history of cannabis use and those without a history of cannabis use?

Although in this thesis we found that schizophrenia patients with a history of cannabis use faced a significantly higher burden of inpatient care, both psychiatric and somatic, we did not find that a history of cannabis use increased the risk of death in subjects with psychotic disorders. We were limited in this regard in that there are no data on treatment for psychotic disorders or substance abuse in the inpatient register. The introduction of second-generation antipsychotic agents during the 1990s may have decreased the risk of death among cannabis users, as has been suggested in a review by Wobrock et al. (93), where second-generation antipsychotic agents were found to have greater efficacy in reducing substance use compared with first-generation antipsychotic agents.

Is there a difference in mortality between Swedish conscripts with a history of cannabis use and those without a history of cannabis use?

We found in this long-term follow-up of male conscripts that subjects with a history of heavy cannabis use had significantly higher risk of death (40%) compared with those without a history of cannabis use. The association persisted after controlling for several possible confounders.

The relation between cannabis use and cancer has been investigated in a number of reviews (94, 95). The existing literature concludes that the evidence is conflicting, but there is reason to suspect that cannabis use can cause some forms of cancer, e.g., lung cancer. In relation to cardiovascular fatalities related to cannabis use, the results indicate that cannabis may cause

death among individuals with existing vulnerability (96, 97), but more evidence is needed before any firm conclusion can be drawn.

Cannabis use has also been associated with fatal collisions (98), and is a key element in the "gateway drug theory" that postulates that cannabis use can facilitate the subsequent misuse of other drugs (98), both of which can contribute to increasing the risk of death among users.

Recent global-burden-of-disease studies (3, 61) have recognized a limitation to capturing some commons disorders, such as cannabis dependence, that may contribute to years of life lost to premature mortality. Increasing awareness of the negative effects of cannabis use and the inclusion of more specific diagnoses related to cannabis, such as cannabis-induced psychotic disorder in the ICD-10 and DSM-IV, can help to identify more adverse effects of cannabis use, which may contribute to years of life lost due to premature mortality.

6 Methodological considerations

The studies in this thesis have some major strengths: First, the Swedish conscript survey uses what to date is the largest and longest population-based cohort with data on cannabis use, and also on a number of social and personality background factors. Second, this is still the only population-based cohort with enough power to assess schizophrenia as a specific outcome, and also a broader range of schizophrenia-spectrum disorders. Third, we have a homogeneous study population, which enables analyses of the lifetime prognosis of schizophrenia in relation to background factors.

Several methodological issues need to be taken into consideration. First, we are constrained by having data regarding use of cannabis only before conscription, it is possible that other risk factors after baseline influence our results such as risky behaviour, use of alcohol and use of other drugs. Second, only males were included. Since the incidence of schizophrenia, other psychoses and depression can vary between men and women, it would be valuable to assess the associations also in women. Third, identification of diagnoses of schizophrenia, other psychoses and depression was limited to cases in inpatient care, so our findings may not be applicable to milder forms of psychosis and depression that do not require hospitalization. Fourth, we are restricted by not having data regarding treatment for schizophrenia in the inpatient register and by the association of cannabis with decreased adherence to treatment. Further studies are needed in order to clarify whether adherence to treatment explains the association between cannabis use and a poorer clinical outcome in schizophrenia, as suggested by Miller et al. (90). Fifth, we are limited in that we did not have information in hereditary factors. Studies suggesting interaction between cannabis and certain genes (99), e.g., the AKT1 gene (100) and the COMT gene (101), may help to explain the associations of cannabis with psychotic disorders.

Exposure

The validity of self-reports on cannabis use can be questioned. Since such reports were part of conscription examination, it is possible that conscripts would under-report since drug use indicates deviant behaviour, but also that they might over-report in order to be exempted from compulsory military training. The prevalence of cannabis use in the age group is, however, consistent with those found in school and other surveys carried out in Sweden around that time (6).

The validity of the data on cannabis use in the conscript surveys has been previously assessed to be adequate (102, 103). Further, we investigated the number of hospital admissions with a diagnosis of drug addiction during the follow-up period, and found a high correlation between level of cannabis use at conscription and later hospital admission for drug abuse.

Outcomes

Regarding the validity of diagnoses in Sweden's National Inpatient Register, several studies have demonstrated adequate validity of the major psychiatric diagnoses used in epidemiological studies. Likewise, the diagnosis of schizophrenia in the inpatient register has been found to be valid (104, 105).

We minimized the possibility of reverse causality by excluding individuals who had a history of psychiatric illness prior to 1973. In Study II, in order to avoid misclassification of outcomes, 11 subjects who had diagnoses of both depression and either schizoaffective disorder or schizophrenia during follow-up were also excluded.

The diagnosis of schizoaffective disorder has questionable validity as a separate clinical entity (106), but is often made when psychotic features are prominent, so we regarded it as important for it to be analysed separately. In this category, we only included subjects with a diagnosis of schizoaffective disorder who did not also have a diagnosis of depression or schizophrenia during follow-up so as to minimize overlapping diagnoses.

7 Conclusions

Our thesis confirms that there is a strong association between cannabis and schizophrenia. Heavy cannabis users retained a higher risk of schizophrenia throughout the follow-up period compared with non-users.

After control for confounders, especially markers of disturbed behaviour during childhood, there was no increased risk of future depression among cannabis users. The evidence for a causal link between cannabis use and depression is less convincing that it is for psychotic disorders.

Schizophrenia patients with a history of cannabis use faced a significantly higher burden of lifetime inpatient care than non-cannabis users. Not only does cannabis increase the risk of schizophrenia, but our findings also indicate that the course and prognosis of schizophrenia may be more severe among cannabis users than in schizophrenia cases in general.

We found that people with a history of heavy cannabis use are at greater risk of premature death than non-users. But a history of cannabis use does not seem to lead to increased mortality among people with psychotic disorders.

8 Implications

The long term effect of cannabis use is much discussed, partly because it is related to the political and ideological debate on the regulation of cannabis. The liberalization of laws on cannabis use in some countries and states, in addition to the decreasing age of first-time cannabis users and the increasing use of high potency preparations are causes for public health concern (68).

Arsenault et al. (58) and Zammit et al. (107) have estimated that elimination of all cannabis use would reduce the incidence of schizophrenia by between 8 and 13%. These estimates are also consistent with, somewhat conflicting, evidence to date on whether an increase in cannabis use is associated with increased incidence of psychotic disorders in the general population (108). Hikman et al. (8) have estimated that cannabis would be responsible for 10% of new schizophrenia cases, rising to 25%, if light use of cannabis also carries the risk. However, recent estimates suggest that cannabis use as a risk factor for schizophrenia is not a major contributor to the population-level burden of disease due to the low prevalence of schizophrenia worldwide (1, 27). There are many different risk factors for schizophrenia operating at the same time (e.g. migration, advanced parental age, social adversity, perinatal complications) and comparable incidence estimates are difficult to obtain

As policy shifts towards decriminalization of cannabis use, it is arguable to hypothesize that cannabis use may increase in the general population, especially among young adults. By extension, so will the number of individuals for whom there will be negative health consequences as pointed out in a recent review in the New England Journal of Medicine (68).

Knowledge of the long-term effects of cannabis is important for many other reasons. They include cognitive effects, psychosocial effects such as early school-leaving, cancer, cardiovascular diseases, suicide, traffic accident, and dependence. Also, there is the therapeutic potential of cannabis. Thus, existing evidence is important for policy and it seems wise to further investigate the positive and negative health consequences of cannabis use.

In particular, as pointed out in a recent paper in The Lancet (109), global health and education policy should have a greater focus on adolescence, when health outcomes can be shaped by the environment.

Even if schizophrenia is not a very frequent disease, it is among the most burdensome and costly illnesses worldwide (29). In the absence of better treatments for schizophrenia, one of the most effective ways of reducing the disability associated with schizophrenia would be to prevent the increasing number of cases associated with cannabis use.

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