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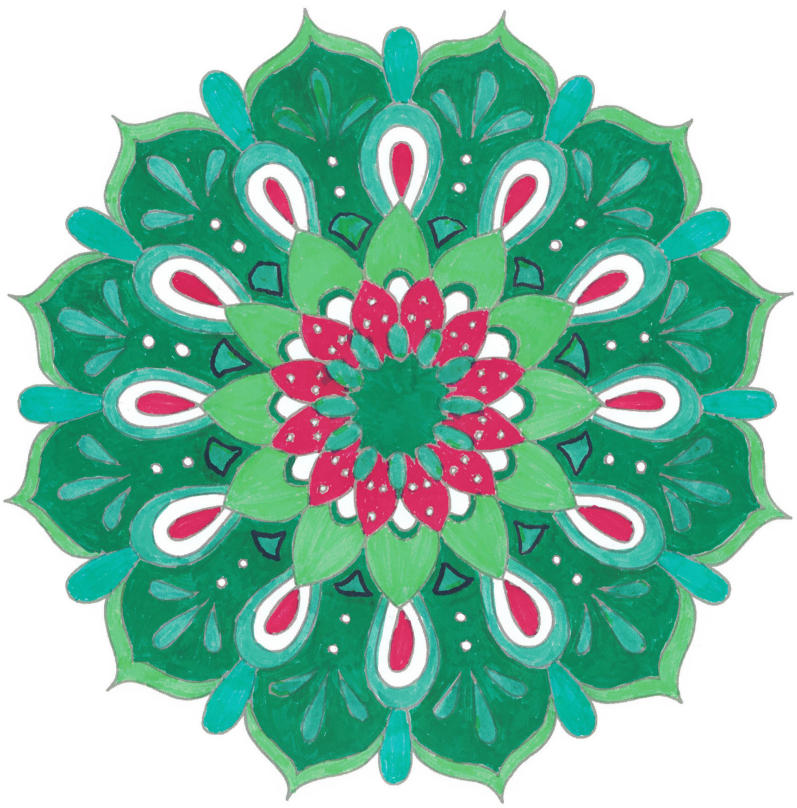
Cannabis use: understanding other illicit drug use, drug-related morbidity and dependence



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CANNABIS USE: UNDERSTANDING OTHER ILLICIT DRUG USE, DRUG-RELATED MORBIDITY, AND DEPENDENCE

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Cannabis use – understanding other illicit drug use, drug-related morbidity, and dependence
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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Most is yet to be discovered.

Therefore, when thou art free from thine immediate task, still labor hard. (QK-94:7)

إلى والدتي الغالية التي غرست المرونة والنزاهة في تربيتي

إلى والدي الغالي الذي شجعني دائماً على تحقيق أهداف سامية

إلى أخواني للاهتمام بي وتمكيني

إلى ولد أخي الجميل الذي جلب السعادة والابتسامة على وجهي

إلى خطيبي لوجوده ودعمه المستمر في هذه الرحلة الطويلة

إلى جميع أهلي وأصدقائي لما قدموه من دعم وتشجيع

To my mother, who instilled resilience and exemplified integrity.

To my father, who always encouraged me to aim high.

To my brothers, for caring and empowering.

To my nephew, for illuminating and completing all my days.

To my fiancé, for your presence, support and for this journey together.

To all my family, for always being supportive, encouraging, nurturing and humorous.

POPULAR SCIENCE SUMMARY OF THE THESIS

Approximately 200 million people worldwide use cannabis, which is a psychoactive substance that affects the brain function, human behavior, and consciousness. Yet, our current state of knowledge about cannabis use in relation to mental health is quite inconclusive. While some associations are well-established; for instance, that cannabis use increases the risk of schizophrenia and other psychotic disorders, other relationships remain to be elucidated. Increased understanding of cannabis use and related health effects is of the utmost importance, in order to facilitate informed decisions with regards to both public health interventions and healthcare. This thesis aimed at increasing the understanding of cannabis use, other illicit drug use, and drug-related morbidity.

In the first study, we used survey data from a longitudinal population-based cohort in Stockholm Region, with linkage to the National Patient Register, and examined cannabis use in relation to other illicit drug use and drug use disorders. We found that cannabis use increased the risk of other illicit drug use at three-year follow-up, with the risk being higher for recent cannabis users compared to lifetime users. We also found that cannabis use did not independently increase the risk for subsequent drug use disorders. This link was rather explained by other illicit drug use.

In the second study, we used data from the longitudinal population-based Women and Alcohol in Gothenburg (WAG) study to examine associations across time between cannabis use and anxiety and depression. Cannabis potency has increased during the last years, as has the risk of developing adverse cannabis-related health outcomes. We found an association between cannabis use and anxiety in both the oldest and youngest cohorts of women, and between cannabis use and depression in the youngest cohort. Thus, the association between cannabis use and depression among the younger women, examined between 2000 and 2015, became more pronounced when adding the effect of period of use.

In the third study, we focused on improving our knowledge of individuals with cannabis use disorder (CUD), that is harmful use of or dependence on cannabis. By examining national health care registers, we saw that there was an increase of CUD diagnoses in Sweden over time, especially among younger birth cohorts. Individuals with CUD were more often male, from younger birth cohorts, with lower education and income than those without CUD. Also, a majority of those with CUD had an additional psychiatric diagnosis. Men and women with CUD exhibited differences in education, income and psychiatric comorbidity. Our subgroup analysis revealed that the two groups with the highest proportions of CUD, were, on one hand, young men with low income and high proportion of other substance use disorders, and on the other hand, young women with high income and high proportion of behavioral disorders.

In the fourth study, we once again utilized national health care registers and examined the extent to which socioeconomic factors and psychiatric disorders affect the risk of CUD readmission into health care. We found that twenty percent readmitted to care during follow-up, and that those with low education, schizophrenia and psychotic disorders, mood-related disorders or personality disorders had the highest risks of readmission. Younger individuals were at highest risk of readmission (aged 18-35 years).

The findings from this thesis provide public health workers and clinicians with scientifically underpinned knowledge regarding the links between cannabis use, other drug use and psychiatric disorders, also demonstrating the impact of socioeconomic factors and psychiatric comorbidity in relation to cannabis use disorder. Our findings may be used to improve cannabis-related care by highlighting individuals with complex healthcare needs, as well as underscoring the importance of comorbidity within psychiatric care.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Över 200 miljoner människor världen över använder cannabis, en psykoaktiv substans som påverkar hjärnans funktion, mänskliga beteenden och medvetande. Vår kunskap om cannabisanvändningens effekter på vår mentala hälsa är begränsad. Även om vissa samband är väletablerade; till exempel att cannabisanvändning ökar risken för schizofreni och andra psykossjukdomar, återstår det fortsatt att belysa andra. Ökad kunskap om cannabisanvändning och relaterade hälsoeffekter är av yttersta vikt, då det kan leda till välinformerade beslut inom såväl sjukvård, som i folkhälsoarbete. Denna avhandling syftade till att öka kunskapen om cannabisanvändning, annan narkotikaanvändning och drogrelaterad sjuklighet.

I den första studien använde vi populationsbaserade enkätdata med länkningar till det nationella patientregistret och undersökte cannabisanvändning i relation till annan droganvändning och drogberoende. Vi fann att cannabisanvändning ökade risken för annan narkotikaanvändning vid treårsuppföljning, och att risken var högre för individer som använt cannabis de senaste tolv månaderna jämfört med individer som endast prövat cannabis vid enstaka tillfällen. Vi fann också att cannabisanvändning inte var en oberoende riskfaktor för senare drogberoende. Detta samband förklarades snarare av annan droganvändning.

I den andra studien använde vi data från den populationsbaserade intervjustudien för att undersöka samband över tid mellan cannabisanvändning och ångest och depression. Cannabis har ökat i styrka under de senaste åren, liksom risken för att utveckla negativa cannabisrelaterade hälsotillstånd. Vi fann ett samband mellan cannabisanvändning och ångest i både den äldsta och yngsta kohorten av kvinnor, och mellan cannabisanvändning och depression i den yngsta kohorten. Associationen mellan cannabisanvändning och depression bland de yngre kvinnorna, undersökta mellan 2000 och 2015, blev mer uttalad när vi lade till effekten av vilken tidsperiod cannabis använts.

I den tredje studien fokuserade vi på att förbättra vår kunskap om individer som fått en diagnos till följd av sitt cannabisbruk inom sjukvården, det vill säga har ett skadligt bruk, eller är beroende av cannabis.
Genom att granska nationella sjukvårdsregister såg vi att det skedde en ökning av cannabis-relaterade diagnoser i Sverige över tid, särskilt bland yngre födelsekohorter. Individer med diagnos var oftare män, från yngre födelsekohorter, med lägre utbildning och inkomst än de utan diagnos. Dessutom hade en majoritet av dem med en cannabis-relaterad diagnos en ytterligare psykiatrisk diagnos. Män och kvinnor med cannabis-relaterade diagnoser uppvisade skillnader i utbildning, inkomst och psykiatrisk samsjuklighet. Våra analyser visade också att de två grupper med högst andel cannabis-relaterade diagnoser bestod av å ena sidan unga män med låg inkomst och hög andel beroendediagnoser, och å andra sidan unga kvinnor med hög inkomst och hög andel beteendestörningar.

I den fjärde studien använde vi återigen nationella sjukvårdsregister och undersökte i vilken utsträckning socioekonomiska faktorer och psykiatriska störningar påverkar risken att återkomma i cannabis-relaterad vård över tid. Vi fann att tjugo procent återinskrevs i sjukvården under uppföljningstiden och att de med låg utbildning, schizofreni och andra psykossjukdomar, affektiva sjukdomar eller personlighetssyndrom hade högst risk för återinskrivning. Unga individer löpte störst risk att återkomma i cannabis-relaterad vård (åldrarna 18–35 år).

Resultaten från denna avhandling ger folkhälsoarbetare och kliniker vetenskapligt underbyggd kunskap om sambanden mellan cannabisanvändning, annan droganvändning och psykiatriska störningar, och visar också på betydelsen av socioekonomiska faktorer och psykiatrisk samsjuklighet i relation till cannabis-relaterade diagnoser. Våra resultat kan användas för att förbättra den cannabisrelaterad vården genom att lyfta fram individer med komplexa vårdbehov, samt understryka betydelsen av samsjuklighet inom psykiatrisk vård.

ABSTRACT

Amid increased prevalence globally of both cannabis use, and cannabis use disorder (CUD), changes of the legal status of use, as well as increased cannabis potency, it is important to increase the understanding about the health effects from using this psychoactive substance. Improved understanding will provide better prerequisites when shaping policies and healthcare systems targeting affected individuals. Thus, the aim of this thesis was to increase understanding of cannabis use, other illicit drug use, drug-related morbidity, and dependence. The studies were based on different sources of information (surveys, interviews, register linkages) and a variety of methodological approaches (longitudinal, cross-sectional, and cluster designs).

Study 1 examined cannabis use in relation to other illicit drug use and drug use disorders. Survey data was used, comprising adults aged 20-64 years from the general population in Stockholm Region (n = 9 733). The results showed that cannabis use did not seem to act as an independent risk factor for later drug use disorders, although cannabis use did increase the risk of other illicit drug use at three-year follow-up. Of the included covariates, alcohol consumption attenuated the associations the most.

Study 2 assessed the relationship across time between cannabis use and anxiety as well as depression. Interview data was used, comprising women born 1955-1993 from the general population in Gothenburg municipality (n = 1 100). The results showed that cannabis using women born in later years were at higher risk of depression and anxiety. The results from the interaction analyses indicated that period of cannabis use increased the risk of depression. Childhood factors (unsafe upbringing and family tensions) attenuated the associations.

Study 3 explored the socioeconomic characteristics and psychiatric comorbidity of individuals with CUD compared to those without. Register data was used to derive the study population, which comprised all individuals born 1970-2000, and registered as living in Sweden sometime between 1990 and 2016 (n = 3 307 759). Four clusters were identified, two of which showed slightly higher proportion of CUD. One of those clusters was characterized by young men with low income and other substance use disorders, and the other cluster was characterized by young women with high income and behavioral disorders.

Study 4 examined CUD readmissions and the influence of socioeconomic factors and psychiatric comorbidity on the risk of being readmitted to healthcare for a CUD diagnosis. Register data was used to derive the study population, which comprised individuals with a CUD diagnosis born 1950-1999, and registered as living in Sweden sometime between 2001 and 2016 (n = 12 143). The results showed that CUD visits mainly took place in the outpatient care (~80%), and that low education, schizophrenia and psychotic disorders, personality disorders, or mood disorders increased the risk of CUD readmission the most. Individuals aged 18-35 years were at higher risk of readmission.

In conclusion, the findings in this thesis show associations between cannabis use, other illicit drug use and psychiatric disorders. Those reporting cannabis use or are diagnosed with CUD are primarily younger individuals, and mainly men, who also suffer from other substance use disorders. On the other hand, women who use cannabis or are diagnosed with CUD are often diagnosed with mood-related disorders, neurotic and stress-related disorders, and behavioral disorders. Risk of being readmitted to healthcare for a CUD diagnosis was highest among young individuals, those with only primary education, schizophrenia and other psychotic disorders, mood-related disorders, or personality disorders. The implications of these findings are of relevance to healthcare, as they inform on the complex healthcare needs of individuals with CUD and their psychiatric comorbidity/multimorbidity – which in turn may affect the risk of readmission. Young individuals are central with regards to cannabis use and CUD. Additionally, since women, to a larger extent than men, visit healthcare for a variety of mental health problems, their possible substance use disorders may be overlooked, hence particular attention should be given to these women.

LIST OF SCIENTIFIC PAPERS

I. **Rabiee R,** Lundin A, Agardh E, Forsell Y, Allebeck P, Danielsson A-K. Cannabis use, subsequent other illicit drug use and drug use disorders: A 16-year follow-up study among Swedish adults. *Addictive Behaviors*, 2020;106:(106390).

II. **Rabiee R,** Lundin A, Agardh E, Hensing G, Allebeck P, Danielsson A-K. Cannabis use and the risk of anxiety and depression in women: A comparison of three Swedish cohorts. *Drug and Alcohol Dependence*, 2020;216(108332).

III. **Rabiee R,** Lundin A, Agardh E, Allebeck P, Danielsson A-K. Exploring cannabis use disorder in relation to socioeconomic characteristics and psychiatric comorbidity: A cluster analysis of 3 million individuals born in 1970-2000. *Submitted.*

IV. **Rabiee R,** Sjöqvist H, Agardh E, Lundin A, Danielsson A-K. Risk of readmission among individuals with cannabis use disorder during a 15-year follow-up: The impact of socioeconomic factors and psychiatric comorbidity. *Submitted.*

The individual studies will be referred to by their Arabic numerals throughout the thesis.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AUDIT	Alcohol Use Disorders Identification Test
CI	Confidence Interval
CUD	Cannabis Use Disorder
DSM	Diagnostic Schedule Manual
DUDIT	Drug Use Disorders Identification Test
HR	Hazard Ratio
ICD	International Classification of Diseases and Injuries
LISA	*Longitudinell integrationsdatabas för sjukförsäkrings- och arbetsmarknadsstudier* (Longitudinal Integrated Database for Health Insurance and Labour Market Studies)
MGR	Multi-Generation Register
NPR	National Patient Register
OR	Odds Ratio
PART	*Psykisk hälsa, Arbete och Relationer* (The Mental Health, Work, and Relations study)
PS	Psychiatry Sweden
TPR	Total Population Register
VAL	*Vårdanalysdatabaserna*
WAG	Women and Alcohol in Gothenburg

1 INTRODUCTION

1.1 BRIEF HISTORICAL OVERVIEW

Cannabis is perhaps one of the most controversial psychoactive substances of the 21st century thus far, at least when following the public discourse, academic advancements, and legislative changes in several countries. The commonly cited introductory phrase in research articles and reports of *cannabis being the most consumed illicit drug worldwide*[1] [e.g., 1–4] echoes and motivates research with varying approaches and points of departures. Although, examples mainly come from high-income countries of the so-called West (i.e., Europe, North America, Australia, and New Zealand) [e.g., 5], consequently reflecting where the main body of research on cannabis use in general populations is based. Of course, that is likely reflective of political milieu, resources, interest, and opportunity rather than other factors – a view supported by evidence of increased research on cannabis use also in low- and middle-income countries [5]. Historically, cannabis was *de facto* first documented in the so-called far East (i.e., today's Asia) [6–8].

Cannabis (from the plant family *Cannabaceae*) has three primary varieties; *Cannabis sativa*, *Cannabis indica* and *Cannabis ruderalis* [7,9], where the latter is often used in hybrids and rarely on its own [6]. The most commonly used are thus *C. sativa* and *C. indica*, with > 700 different strains existing [6]. Cannabis originates from Asia (most likely Western and Central Asia), and later gradually spread to (North) Africa, Europe, and the Americas [1,7,9].

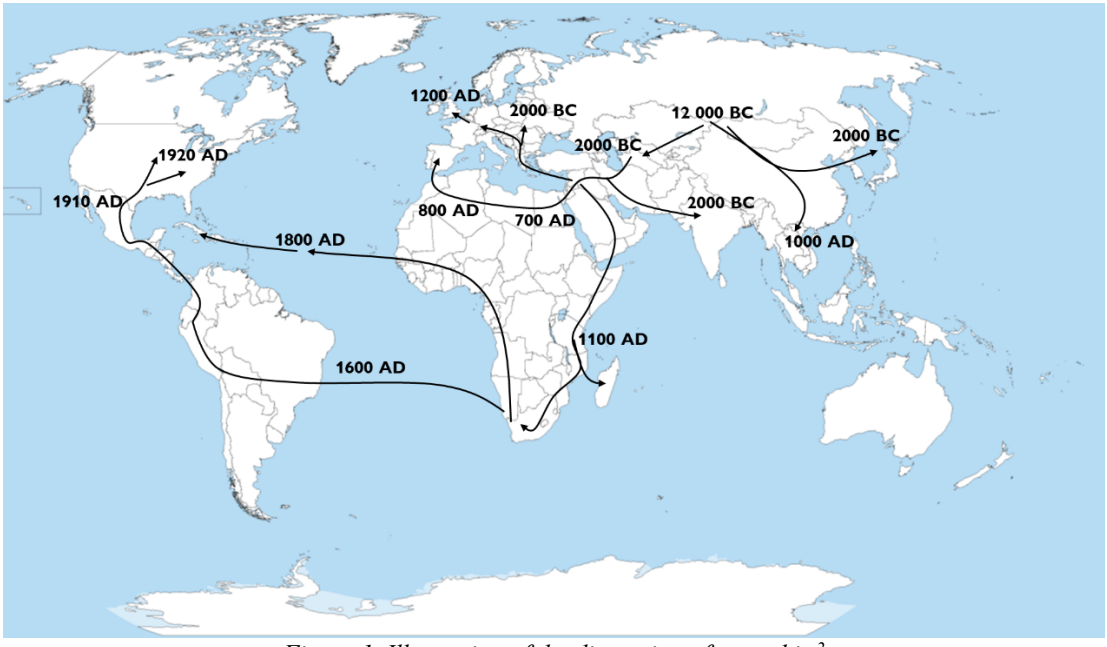

Figure 1. Illustration of the dispersion of cannabis.[2]

[1] Paraphrased – the sentence usually reads; *Cannabis is the most consumed illicit drug in the world.*

[2] Figure 1 adapted based on information from: Warf, B. High Points: An Historical Geography of Cannabis. Geographical Rev. 2014;104(4):414–38.

Several names for cannabis and its different strains exist, with some of the most common being weed, pot, ganja, and kush (often pure *C. indica*), although many more exist. The main forms of preparations are bhang (a paste-like texture), hashish (compressed trichomes), hash oil, and leaves/buds, and the common methods of consumption are usually smoking, vaping, or orally ingesting (edibles or oil drops) [6]. These different preparations and ways of consumption are, however, rarely reported in studies, and the literature related to cannabis use often discards preparation or mode of consumption.

With cannabis making its way across the world, numerous historical records suggest both medicinal and recreational use [9,10], especially during the late 1800s and early 1900s. International control and regulation of psychoactive substances has been in place since the Opium Convention in 1912, where cannabis was included in 1925 after the scope of the treaty expanded [10]. Since then, cannabis research has inevitably been affected by the international and national regulations, where claims by critics of medicinal benefits have been balanced by claims of the harmful effects and the need for control [7].

As a result, most research on cannabis use has been conducted while it has been (and largely continues to be) an illicit drug, an although great advancements have been made, this has likely impacted the research. Certainly, studying an illicit behavior in the general population introduces some inherent difficulties, whereby participation and response rates may be negatively influenced, and respondents may not answer truthfully to questions about their engagement in illegal activities.

1.2 FOCUS OF THE THESIS

Irrespective of the legal status of this plant with psychoactive components, it is clear that cannabis use will have health effects. In this thesis, potential health benefits of the cannabis plant are not ruled out, they are merely out of focus. Instead, the focal point is on the harmful effects of cannabis use, with an emphasis on increasing the understanding of the link between cannabis use, other illicit drugs, cannabis use disorder (CUD), and psychiatric morbidity.

2 BACKGROUND

2.1 CANNABIS AS A PSYCHOACTIVE SUBSTANCE

The cannabis plant comprises a main psychoactive substance called Δ-9-tetrahydrocannabinol (THC) which causes the euphoric effect (a "high") and is addictive [11,12]. Another main substance is cannabidiol (CBD), which mitigates the effect of THC and contributes to therapeutic effects [11,12]. Acute effects of cannabis use can be both positive and negative. Positive acute effects include sense of pain alleviation and joy [13,14]. Negative acute effects on the other hand, include slower reactivity and decreased control of motor functions, as well as possible anxiety, paranoia, and psychotic episodes [13,14].

While cannabis use has increased globally in the past decades [15], its potency has as well [16,17]. In recent years, THC has appeared in higher levels both in the confiscated cannabis across the world and the cannabis sold in legal outlets – the potency in todays consumed cannabis has thus risen [16,18]. In the late 1970's, the THC percentage was less than one percent (in USA and Canada) while reaching up to 15-20% in 2016-17 [16,17,19,20]. Similar results have been found in Europe and a recent study from Denmark showed a 3-fold increase in THC concentration between 2000 (8.3%) and 2017 (25.3%) [21,22].

Higher THC concentration in cannabis have been linked to several negative health outcomes, including psychotic disorders [15], poorer addiction outcomes [23] and depression [12]. It has been hypothesized that the increase in THC over time may contribute to increased prevalence of depression and anxiety [24,25]. Considering that THC concentration may partly explain the relationship between cannabis use and anxiety as well as depression [25,26], studies comparing these associations over time as well as comprising more recent data on cannabis use are required.

2.2 CANNABIS IN SOCIETY

Internationally, cannabis use is reported by some central sources of information, including the World Health Organizations survey (ATLAS survey), United Nations Office on Drugs and Crime (from e.g., World Drug Reports), the European Monitoring Center for Drugs and Drug Addiction (based on e.g., European Web Survey on Drugs), as well as European School Survey Project of Alcohol and Other Drugs, National Epidemiologic Survey on Alcohol and Related Conditions, Substance Abuse and Mental Health Administration and National Survey on Drug Use and Health. These sources provide regular, reliable information about cannabis use and are widely utilized in research.

Cannabis is the most consumed illicit drug worldwide with an estimated 200 million users [27,28]. Generally, cannabis is considered an illicit drug, although in recent years several countries have started to legalize its use (e.g. Uruguay, Canada, and several states in the US). The prevalence of cannabis use varies greatly between countries, with the highest annual use being observed in North America at 13.8% [29] (with e.g. Canada at 15% [30]) and Oceania at 10.9% [29] (with e.g. New Zealand at 11% [31] and Australia at 10% [32]). In Sweden, it has been estimated that about 10-12% have ever used cannabis, with a quite stable past year

prevalence of 2-3% [33]. Above all, younger people are using the drug; in Sweden 21% of those aged between 16 and 29 report having ever used cannabis [33]. A slight increase has been observed in the past year prevalence since 2009 especially among those aged 16-29 years [33].

Exposure to cannabis use in early life has greater adverse health effects than being exposed in older age, and exposure to cannabis use in adolescence has been shown to increase the risk of negative effects on e.g., educational attainment [e.g., 23] – which in turn is a key determinant for health [35]. Furthermore, cannabis use has been shown to increase the risk of experiencing social disadvantage such as receiving disability pension [36]. Several studies on cannabis use and its link to other illicit drug use have been carried out [13], importantly so, since understanding this link has implications for both prevention and healthcare services. Such implications may, for instance, be underpinnings for formation of healthcare services for patients with any drug use or drug-related problems. Although the association between cannabis use and other illicit drug use has long been under study, there is still uncertainty regarding the extent to which cannabis is to be considered a risk factor.

2.3 THEORIES OF DRUG USE PROGRESSION

Three theories of drug use progression are recurrently mentioned in the scientific literature [37], namely the route of administration model, the theory of common liability and the gateway sequence theory [38].

The route of administration model [e.g., 26] puts special emphasis on the route of consumption, where the method of using one drug may account for the use of another. For example, smoking tobacco increases the risk of initiating use of cannabis administered in the same manner, or injecting one drug may increase the risk of initiating the use of another injection drug. The theory of common liability [e.g., 28] rather suggests shared factors that increase one's vulnerability/susceptibility to use other illicit drugs and develop dependence or drug use disorders. These common factors address the mechanisms and characteristics of development of dependence or drug use disorders, an example can for instance be proneness to deviant behavior [e.g., 29].The gateway sequence theory is perhaps the theory that has influenced debates regarding drug policies the most [41]. This long-debated theory was first proposed by Kandel et. al. in the 1970's and has continuously been tested and replicated [41]. It proposes an 'invariant sequence' in the progression of drug use (starting from alcohol & tobacco to cannabis use, further onto other illicit drug use, ultimately ending in harmful use of and dependence on drugs) [38]. Thus, the gateway theory raises the question of whether cannabis use in itself increases the risk for other illicit drug use and drug use disorders.

It is, however, unclear if one theory is able to explain the mechanisms of drug use progression better than any other. Thus, the association between cannabis use and drug use disorders remains unclear. Although an association between cannabis use and the subsequent use of other illicit drug use has repeatedly been observed [e.g., 3,31,32], the predictors of drug use progression (from cannabis to other illicit drugs and subsequent harmful drug use and/or drug dependence) are largely unknown [43].

2.3.1 Cannabis use in relation to other drug use

The link between cannabis use and other illicit drugs, as well as multidrug or polydrug use (i.e., using different substances interchangeably) is common [13]. It has been suggested that although a range of early life circumstances that put individuals at greater risk (e.g. parental drug use, childhood abuse, and conduct disorder), the use of cannabis in late adolescence emerges as the strongest risk factor of other illicit drug use and dependence [42]. This is also supported by twin studies, which aim to rule out genetic and environmental factors which may influence the association [39,44,45]. These have shown early-onset cannabis users to be at two to six times greater risk of other illicit drug use and drug use disorders, compared to their non-using twin. Users were also twice as likely as their non-using twin to meet criteria for dependence [44,46].

As part of the drug use progression, health outcomes such as mental illnesses as consequences of cannabis use have been investigated [13]. While some relationships are relatively well-established, such as the association between cannabis use and schizophrenia [47], other associations are yet to be unpacked.

2.4 CANNABIS USE IN RELATION TO PSYCHIATRIC DISORDERS

The terms comorbidity, multimorbidity and co-occurring diagnoses are sometimes used interchangeable, although they are not exactly synonymous. Comorbidity was first coined in 1970, defining an additional disease present or developing during the course of an individual during the study period [48]. Multimorbidity followed shortly after (from 1976) and was commonly used to describe individuals with multiple (two or more) chronic conditions [48,49]. In this thesis, the term comorbidity is used to indicate a main focus on disorders due to cannabis use in relation to other psychiatric disorders that may have occurred or been diagnosed at different time points.

Previous studies have shown that cannabis use may lead to several adverse health outcomes, such as poorer cognitive function [50,51], depression [52], psychoses [47], and cannabis use disorders [13,38,53]. Increasing number of studies show that cannabis use is associated with a variety of psychiatric diseases such as anxiety, depression, and dependence [13,24,54], while, at the same time, studies also report absence of these associations [e.g., 42,43]. The debate regarding the possible negative health effects of cannabis use has been long-standing, yet consensus has not been achieved. Common limitations in previous studies have been restricted study populations, inability to rule out reverse causation, and limited confounding control. It has recently been highlighted that further research is needed regarding the effect that cannabis use might have on mental health, not the least longitudinally [13]. Despite this, uncertainty remains as previous studies have produced somewhat mixed results. Some have reported an independent risk increase of cannabis use on drug use disorders [e.g., 44], while others have emphasized other overlapping risk factors, for example conduct disorders [58] and adverse childhood conditions [59]. Therefore, it is still unclear to what extent the association between cannabis use and subsequent other illicit drug use is an effect of the drug itself, reflects characteristics of the users, or is a consequence of other uncontrolled confounders [60].

It has been shown that up to one-third of cannabis users may develop CUD [61]. Studies have reported that CUD is highly prevalent and available literature has identified some characteristics of and potential risk factors for CUD. For instance, CUD has been reported to be comorbid (e.g., with other substance use disorders and mental health problems) and characterized by low quality of life [61,62]. The prevalence of CUD has also been shown to be greater among those with low income [63,64]. However, of the few studies that have been conducted on CUD and comorbidity to date, the majority have been conducted in the US. Thus, replications of studies on this topic are needed in other contexts [64].

Importantly, a study from the US found the transition rate from cannabis use to CUD to be higher among those with a mental illness (such as anxiety, mood, psychotic, or personality disorder) [61]. In particular, individuals with psychotic and personality disorders have been associated with higher rates of transition from use to dependence, where more than half of the cannabis users studied developed CUD [61]. Certain sex differences have also been observed, where men have been shown to have higher prevalence of CUD than women [63,64]. Two studies reported higher rates of other drug use disorders and antisocial personality disorder among men with CUD [63,64], whereas women have been found with higher rates of mood and anxiety disorders [62]. Differences in severity of CUD between the sexes and their association with different mental illnesses have also been observed [64]. For instance, mild CUD among men has been shown to be associated with persistent depression, moderate CUD among men and mild CUD among women with generalized anxiety disorder, and moderate CUD among women with post-traumatic stress syndrome [64].

2.5 CANNABIS USE DISORDER & CANNABIS-RELATED CARE

Regular cannabis use over time is required and assumed in order to develop conditions like harmful use of, or dependence on cannabis – together defined as cannabis use disorder (CUD) in this thesis. This may follow either operational criteria from the International Classification of Disease (in version ICD-10 by the World Health Organization [65]), or they may follow the DSM criteria by the American Psychiatric Association, where DSM-5 is the latest version and DSM-IV its predecessor [66]. The diagnostic criteria are available in appendix (Appendix 1).

The DSM-5 provides descriptions of 11 symptom criteria regarding impaired control, social impairment, risky behavior, and physiological adaptation. Having 2-3 symptoms indicates a mild CUD, the presence of 4-5 symptoms indicates moderate CUD and 6 or more symptoms indicate severe CUD [60]. The predecessor, DSM-IV, included abuse (oriented towards social problems) instead of harmful use (a rather medical term). That version required the fulfillment of one criterion out of five to be met for an abuse diagnosis, and three out of six criteria for cannabis dependence – both within a 12-month period. The ICD-10 provides criteria of symptoms harmful use and dependence, with the specific codes F12.1 (harmful use) and F12.2 (dependence).

Studies from the US have reported younger age-groups (18-25 or 18-29) to be at higher risk of CUD compared to their older counterparts [63,67]. Furthermore, another recent study from the US demonstrated that adolescents (12-17 years) had a higher 12-month CUD prevalence following cannabis use compared to young adults (18-25 years), which was consistent on a

yearly basis up to four years after cannabis use was initiated [68]. This study also reported that the prevalence of CUD ranged from 10-20% among adolescents and between 5-10% among young adults.

When exploring the development of CUD, previous studies have shown considerable remission rates of around 80%, with slightly higher remission among women than men [62,69]. Similarly, a more recent study showed that approximately 67% of individuals with a CUD diagnosis remitted at a 3-year follow-up, while 33% remained diagnosed [70]. However, in this study CUD was measured by self-reports, which may have biased the results. It has been shown that women are more likely to remit compared to men [62], and also that they recover at a faster rate [69] as well as being younger at remission compared to men [62]. In study from the US, the mean duration from CUD onset to recovery was reported at around 32 months, however men showed a significantly longer duration compared to women; 41 months compared to 25 months [69]. However, this study suffered from unequal sampling strategy and high attrition during follow-up, which may have biased the results.

A recent systematic review on the health care utilization of people who use illicit drugs, illustrated the lack of studies focusing on cannabis – the authors were able to identify only eight unique study populations – with a majority being from the US, which inhibited further analysis [71]. The review also showed that twelve months was the most common period to study. The literature on remission from CUD is thus scarce, and future studies with longer follow-up times and including e.g. time-varying variables, such as educational attainment or socio-economic position, are warranted [72].

In Sweden, the responsibility for healthcare sits at regional level while social services is at a municipality level. This affects the care and treatment offered to individuals with CUD, and has been criticized as it gives rise to problems regarding responsibility and commitment [73]. With this in mind, together with the limited body of research on individuals with CUD, it is important to study individuals in CUD-related healthcare. By studying healthcare registers, which in Sweden inevitably captures healthcare utilization, the understanding of how CUD may develop over time could be highlighted to some extent, which would give greater insight into the current situation as well as gaps of knowledge.

2.6 METHODOLOGICAL REMARKS

Studying illicit behaviors may be difficult and it is fair to assume that methodological challenges may arise with data collection. In Sweden, survey data from the Public Health Agency show quite stable prevalence of cannabis use [33]. This stability indicates a general level of consumption in the population, although still being susceptible to selective sampling and non-response. In general, non-responders have been characterized by being male, young, unmarried, and less educated [74] as well as consuming more alcohol and using other illicit drug to a larger extent than respondents [14], furthermore being at higher risk of drug-related morbidity and mortality compared to responders [74]. This possible selection bias and attrition is important to acknowledge of when studying cannabis use and related morbidity, prompting caution when interpreting results.

2.7 SUMMARY OF RESEARCH GAPS & RATIONALE

There have been repeated observations of the association between cannabis use and other illicit drug use [13,43], but much less is known about the link to drug use disorders. While some studies have reported that cannabis may act as an independent risk factor for drug use disorders [57], others have stressed the importance of overlapping risk factors such as psychiatric disorders [58,75] and childhood conditions [76]. As such, it is not determined whether cannabis use is an independent risk factor for continued harmful drug use longitudinally [60]. Common limitations in previous research have been restricted samples, either by size or type (e.g., clinical), or inadequate confounding control, and short follow-up periods [13]. With this in mind, studies that allow control for a range of factors, such as adverse childhood circumstances, educational attainment, socioeconomic position, and alcohol use, in combination of larger, longitudinal cohorts are warranted.

The increased potency of cannabis over time [ref] has given rise to questions regarding its potential effect on health. A recent large-scale study showed that high-potency cannabis increased the risk for psychotic disorders [15,77]. Such findings inspire further research on the effects of cannabis potency, and it has been suggested that THC concentration plays a role in the development of mental health problems such as anxiety and depression, yet the associations are still unclear [25,78]. Considering that cannabis potency may in part explain the relationship between cannabis use and anxiety and depression [25,26], studies comparing these associations over time, covering older as well as more recent data on cannabis use, are needed. Especially since these disorders affect large proportions in populations across the world and especially women [79].

CUD is currently one of the main reasons for individuals seeking substance use treatment, and the demand for cannabis use-related treatment has increased in all Nordic countries [80]. Still, no previous study has looked into the individuals seeking healthcare for CUD in Sweden. Knowledge of healthcare utilization of individuals with CUD, and information on trends regarding this utilization, is necessary for planning and implementation of appropriate prevention and healthcare measures. In spite of the scarcity of studies, CUD has been shown to be comorbid [52,81,82] and some sex differences with regards to remission have been observed [69]. The risk of CUD relapse has also been shown to be higher among individuals with low education or income [83]. Furthermore, a limited number of studies have examined CUD and healthcare utilization, and most of those studies have been US based. Therefore, it is important to understand individuals with CUD and psychiatric comorbidity in other contexts. Additionally, previous studies have looked at inpatient care [84,85] whereas information from the outpatient care has not been included. We have limited knowledge about the extent to which individuals with CUD are readmitted to healthcare in Sweden, or whether socioeconomic factors, or certain comorbid psychiatric disorders are important contributors to the risk of readmission.

3 RESEARCH AIMS

The overall aim of this thesis is to increase the understanding of cannabis use, other illicit drug use, drug-related morbidity. Throughout the thesis, special focus is placed on cannabis use (on different levels, be it lifetime use or heavy use resulting in cannabis dependence), and its associations with different psychiatric disorders.

Specific aims and research questions for each study:

STUDY 1

We aimed to examine the association between cannabis use and subsequent other illicit drug use and drug use disorders (harmful use and dependence), and answer the following research questions:

a) To what extent does cannabis use increase the risk of other illicit drug use?

b) To what extent does cannabis use increase the risk of drug use disorders, when compared to other illicit drug use?

STUDY 2

We aimed to examine the association between cannabis use and anxiety and depression, and to find out whether any such association changed over time – which could be attributed to the increased THC concentration in recent years.

STUDY 3

We aimed to study individuals diagnosed with CUD in Sweden between 1990 and 2016, and answer the following research questions:

a) What is the number of CUD diagnoses registered in healthcare across different age groups in Sweden between 1990 and 2016?

b) What characterizes individuals diagnosed with CUD in comparison to individuals without CUD, with regard to sociodemographic characteristics and other psychiatric disorders?

c) To what extent does CUD cluster among individuals with certain sociodemographic characteristics, and psychiatric comorbidity?

STUDY 4

We aimed to characterize CUD readmissions as well as examine the risk of CUD readmission, and answer the following research questions:

a) What characterizes readmissions due to cannabis use disorder with regards to frequency, severity of cannabis use disorder, socioeconomic factors, psychiatric disorders and health care provider?

b) What is the risk of readmission after initial diagnosis of cannabis use disorder?

c) To what extent do socioeconomic factors and psychiatric disorders influence the risk of readmission of cannabis use disorder?

d) How does the risk of readmission vary by age?

4 MATERIALS & METHODS

This thesis includes data from three different data sources. An overview is outlined in Table 1 and the relationship between the individual study aims, materials and methods are illustrated in Figure 7.

Table 1. Overview of data sources for each study.

Study	Data source	Sample	Participants	Ages/Birth years	Data collection
Study 1	The Mental Health, Work and Relations study *(Swedish acronym: PART[a])* Survey data with linkage to patient registers	Stockholm Region Men and women General population-based sample	9 733 individuals, including a sub-sample of 7 616 individuals	20-64 years	Baseline 1998-2000 Follow-up 2001-2003
Study 2	The Women and Alcohol in Gothenburg cohort (WAG) Interview data with clinical diagnoses	Gothenburg municipality Women General population-based sample	1 100 individuals, divided into three birth cohorts	Oldest, cohort 1: Born 1955, 1965 Second oldest, cohort 2: Born 1970, 1975 Youngest, cohort 3: Born 1980, 1993	1986-1992 1995-1998 2000-2002 & 2013-2015
Study 3	Psychiatry Sweden (PS) Comprehensive register-linkages	Sweden Men and women Total population register	3 307 759 individuals	1970-2000	1990-2016
Study 4	Psychiatry Sweden (PS) Comprehensive register-linkages	Sweden Men and women Total population register	12 143 individuals	1950-1999	1990-2016

[a] PART - Psykisk hälsa, arbete, relationer

4.1 MATERIALS

The three data sources are of varied types and include surveys, interviews, and national registers. The data used for the respective studies have some overlap, pertaining mainly to register utilization.

4.1.1 The Mental Health, Work and Relations study (PART) – *STUDY 1*

The study population was based on data from the PART study, a general population cohort which includes survey data with linkage to National Patient Register (NPR) [86]. It comprises data on adults aged 20-64 years at baseline in Stockholm, Sweden.

Data collection was initiated between 1998 and 2000 where five, equal-sized, random samples of Swedish citizens residing in Stockholm, were drawn from the Stockholm Region (then; Stockholm County, approximately 858 000 individuals) [56]. Of the invited individuals (n = 19 742), fifty-three percent (53%) responded to the questionnaire (n = 10 441). The respondents were sent a follow-up questionnaire after three years (2001-2003), where the response rate was eighty-three percent (83%, n = 8 613). The data collection was carried out by Karolinska Institutet.

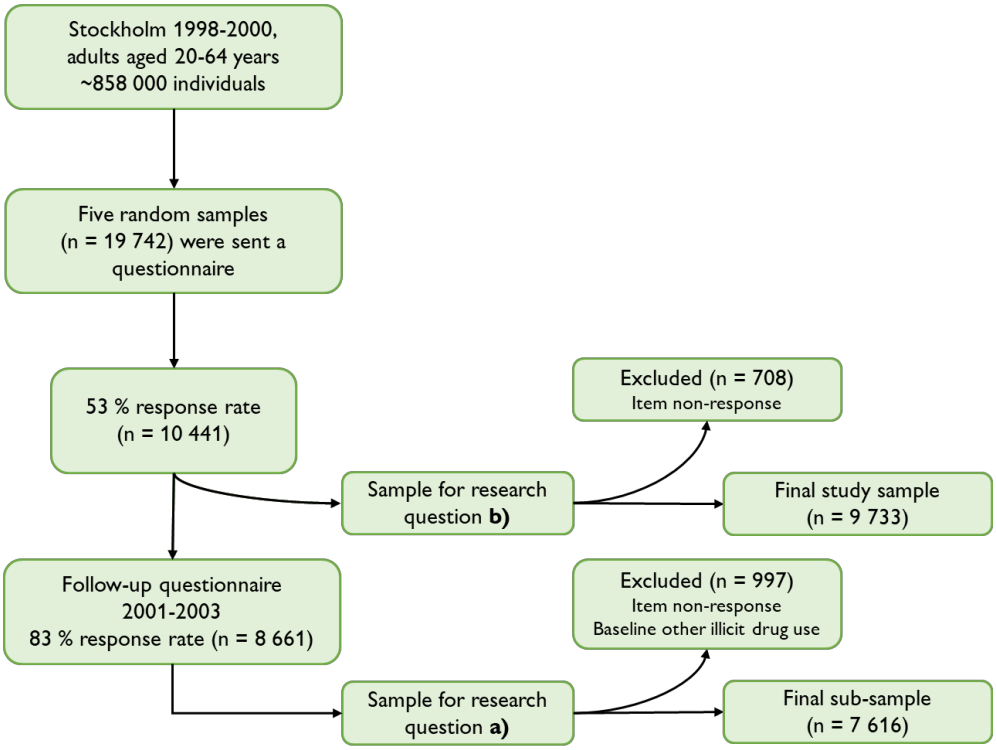

Figure 3. Flowchart of sample from the PART study used in Study 1.

For our study, we utilized data from both baseline and follow-up. We excluded individuals with missing information on study variables. The flowchart above (Figure 1) illustrates the study population used for the research questions in Study 1.

4.1.2 The Women and Alcohol in Gothenburg cohort (WAG) – *STUDY 2*

The study population was based on data from the WAG cohort, a general population cohort, which includes interview data with clinical diagnoses [87–89]. It comprises data on women from selected birth cohorts between 1955 and 1993 in Gothenburg, Sweden.

Data collection was initiated in 1986 where a two-phase sampling strategy was implemented, with the objective to over-sample women with alcohol-related problems. This sampling strategy was carried out in four waves, each wave encompassed the two phases: phase one included screening for alcohol-related problems and phase two included a structured in-person interview. The screening questionnaire was *Screening for Alcohol dependence and Abuse in Women* (SWAG) [87]. Based on the scores from the screening in phase one, a stratified sample was selected for interview. The scores ranged from 0 (indicating *no alcohol-related problems*), 1-3 (indicating *possible alcohol-related problems*), and ≥5 (indicating *probable alcohol problems*). All women from the highest scoring group were invited for interview. Randomly selected women from the two remaining groups, as well as from the non-respondents, were invited for interview. Due to the low response rate in the fourth wave, all women participating in the screening were invited for interview.

The screening for the first wave was initiated in 1986 and interviews took place between 1989-1992. The first wave included all women born 1925, 1935, 1945, 1955, and 1965 (n = 3 130), however we excluded women born prior to 1955 due to few exposed individuals (n = 8). The screening for the second wave took place in 1995-1996 and interviews in 1995-1998. The second wave included women born 1970 and 1975. The screening for the third wave took place in 2000 and interviews in 2000-2002, which included women born 1980. The screening for the fourth wave took place in 2013 and interviews in 2013-2015, which included women born 1993. Different versions of the interview were offered, however we only included women who completed the comprehensive (long) interviews. The flowchart below illustrates the study population used in Study 2.

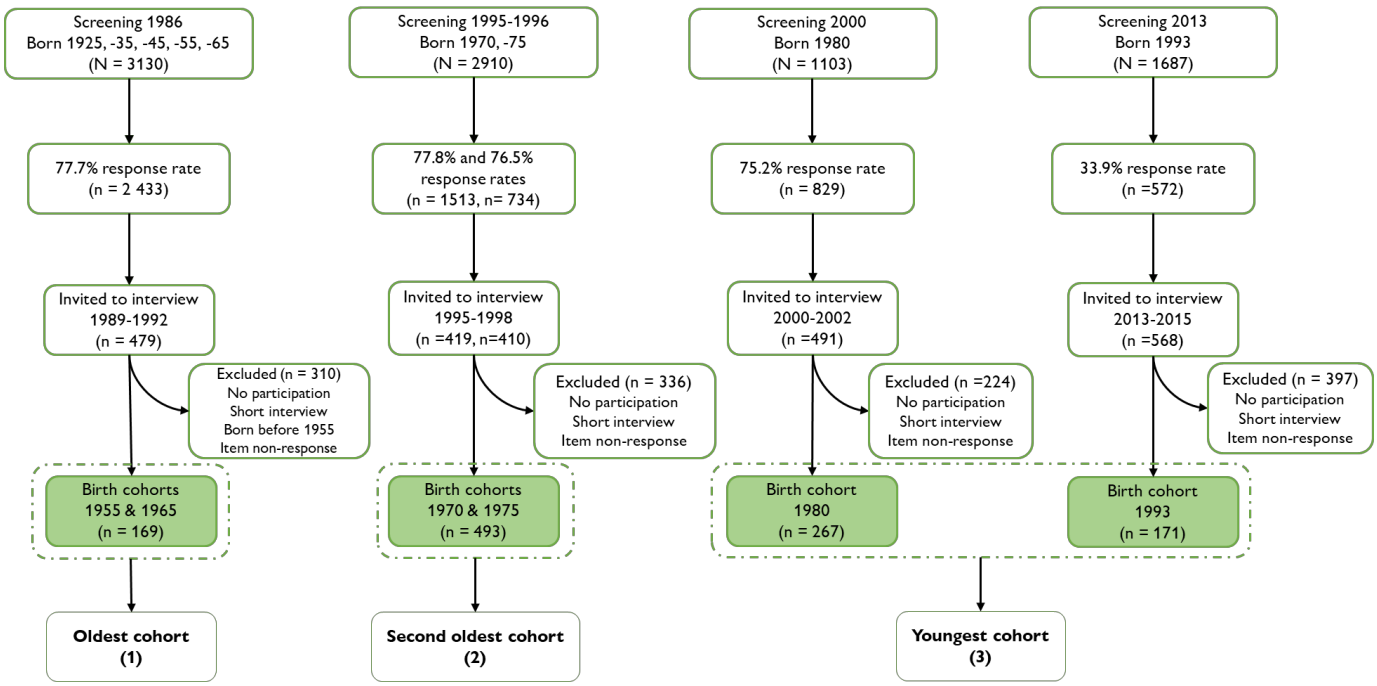

Figure 4. Flowchart of sample from the WAG cohort used in Study 2.

4.1.3 Psychiatry Sweden (PS) – *STUDY 3 and STUDY 4*

Data for studies 3 and 4 were obtained from the PS database, which comprises multiple national registers that are approved for research.

STUDY 3

In Study 3, individuals were identified from the Total Population Register (TPR, variables birthdate and sex) [90], Longitudinal integrated database for health insurance and labour market studies (*Swedish acronym: LISA*[3]) [91], held by Statistics Sweden. The study population comprised all individuals registered in Sweden sometime during 1990-2016 and were born between 1970 and 2000. Individuals were included once they turned 16 years old or at the start of the study period (in 1990), whichever came last. Linkage to the NPR was utilized to obtain information on cannabis use disorder and other psychiatric disorders. For this study, data was used from the in- and outpatient healthcare registers, and for a subset of the population the primary healthcare register in Stockholm *(Swedish acronym: VAL*[4]*)* was also utilized. Unique records of each diagnosis were used. We excluded duplicate records, individuals who died during the study period (obtained from Cause of Death register [92]) and individuals with missing data on sociodemographic factors. Our final study population comprised over three million individuals (n = 3 307 759).

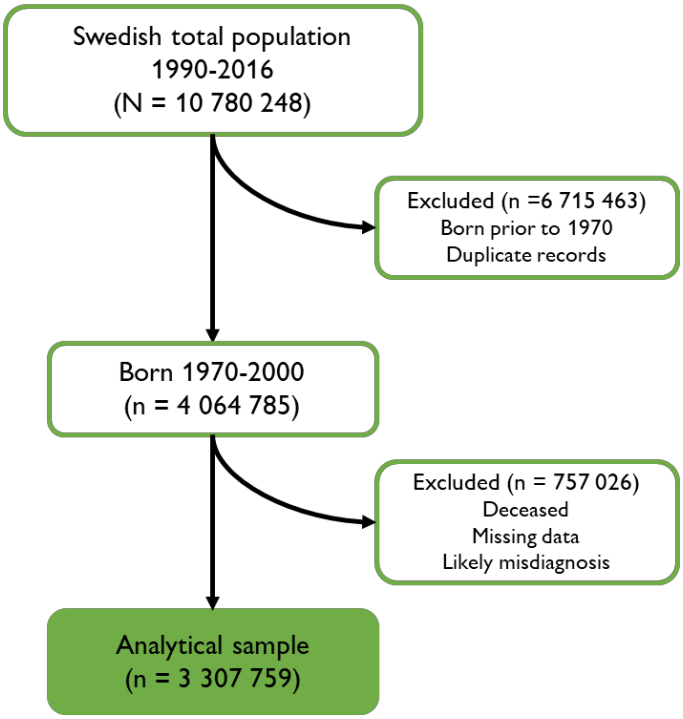

Figure 5. Flowchart of analytical sample from the PS data used in Study 3.

[3] LISA – Longitudinell integrationsdatabas för sjukförsäkrings- och arbetsmarknadsstudier
[4] VAL – Vårdanalysdatabaserna

STUDY 4

In Study 4, individuals were identified from the TPR and linked to NPR and included if they had received a CUD diagnosis, were born 1950-1999, and registered as living in Sweden sometime during 2001-2016. Other psychiatric disorders were also obtained from the NPR. In this study, data from NPR was used during a more restricted time period compared to Study 3, where all diagnoses registered before 2001 were excluded because of better coverage. We further excluded individuals having received a CUD diagnosis before the age of 17 years and individuals with missing data on socioeconomic factors. Our final study population comprised 12 143 individuals.

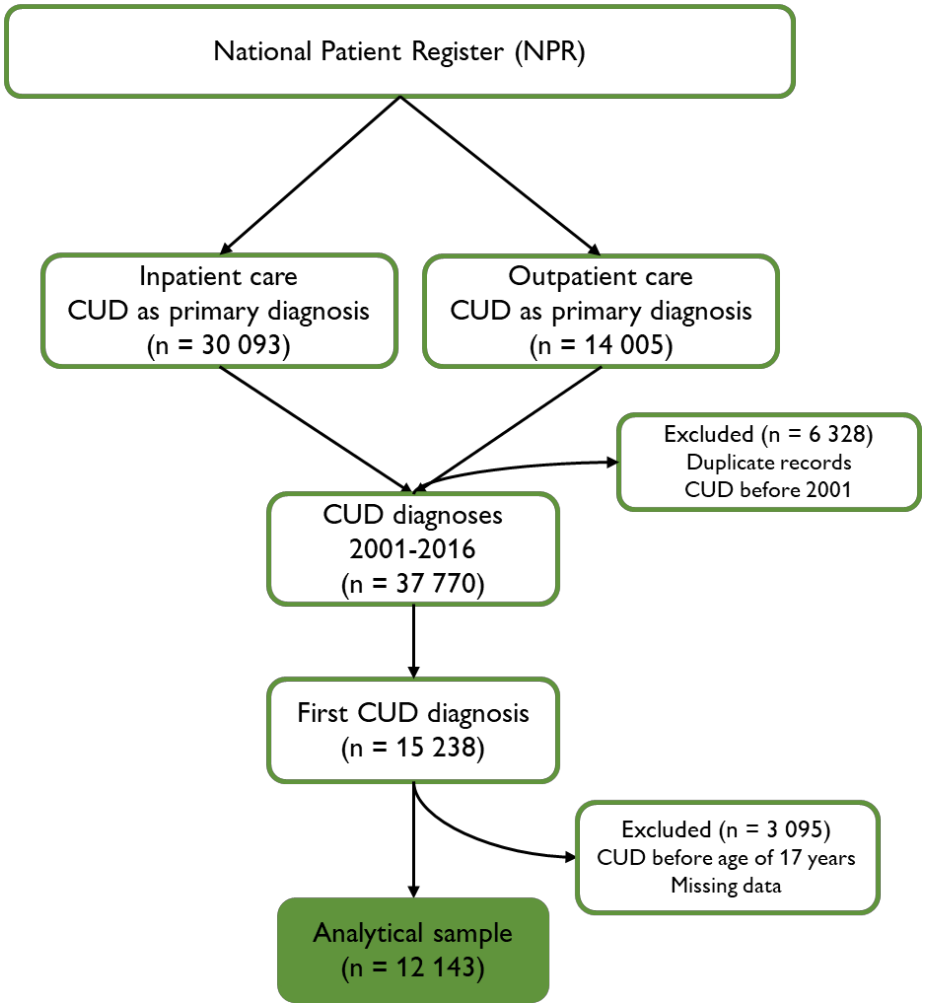

Figure 6. Flowchart of analytical sample from the PS data used in Study 4.

4.2 METHODS

An overview of the individual study aims and methods for each study is available in the figure below (Figure 7).

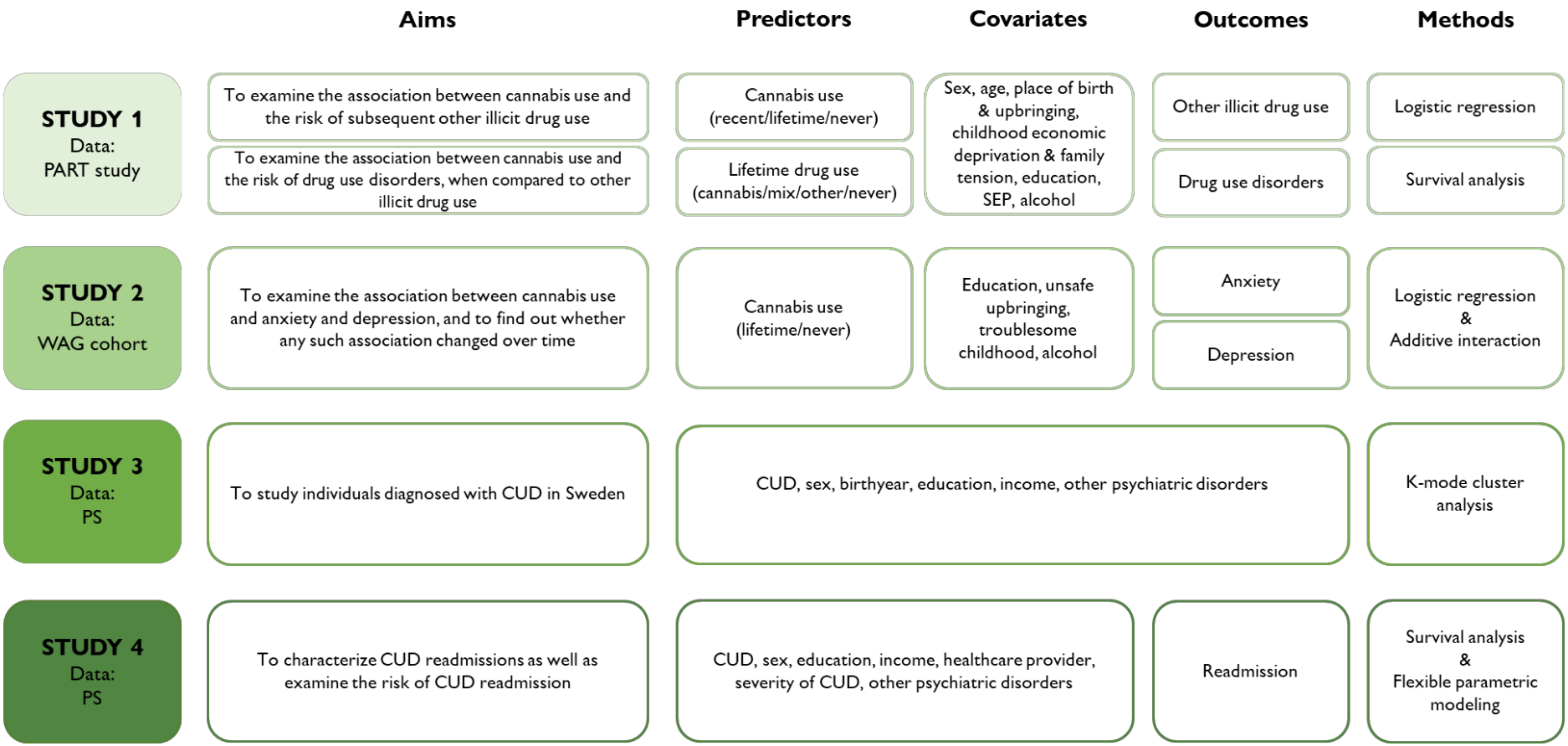

Figure 7. Overview of the individual study aims, materials and methods.

4.2.1 Measures Study 1 (PART)

4.2.1.1 Predictors

Cannabis use was utilized in two ways:

Positive responders to a stem question on the use of illicit drugs (Have you ever used drugs? Yes/no) were in a second question asked which drug they had used, choosing from a list on which cannabis (also defined as hashish or marijuana) was one option.

For the predictor in the first research question, those reporting other illicit drug use at baseline were excluded and the cannabis users were grouped as *never, ever and recent cannabis users* (recent users:<12 months ago, and ever users: more than 12 months ago). For the predictor in the second research question, the full cohort was utilized, and baseline other illicit drug use was taken into account in the operationalization. The predictor was thus ever use of drugs grouped as *never use, lifetime cannabis use, lifetime cannabis and other illicit drug use, and lifetime other illicit drug use (without cannabis use)* respectively.

4.2.1.2 Outcomes

The outcome in the first research question was *other illicit drug use* at follow-up, where the list of illicit drugs in the questionnaire included: central stimulants, e.g., amphetamine; opiates, e.g., opium, heroin, morphine, crack, etc.; hallucinogens, e.g., LSD; cocaine; ecstasy; and 'other'. Participants who answered affirmatively regarding any of these options were grouped as other illicit drug users.

The outcome in the second research question was *drug use disorders* as registered in the NPR, which was defined as first time of diagnosis (in accordance with the International Classification of Diseases, ICD-10) of harmful drug use or drug dependence, in either the in- or outpatient care. Drug diagnoses due to tobacco, alcohol and/or cannabis were excluded since the aim was to investigate any potential risk increase that cannabis use may have on drug use disorders identified through hospitalization. Thus, drug use disorders included due to opioids, sedatives and hypnotics, cocaine, other stimulants, hallucinogens, volatile solvents, multiple drugs, and other psychoactive substances. The specific ICD-10 codes used are listed below (Table 2).

Table 2. Overview of diagnosis included in the operationalization of drug use disorders.

ICD-10 code	Diagnosis
F11.1, F11.2	Opioid use disorder
F13.1, F13.2	Drug use disorder due to sedatives and hypnotics
F14.1, F14.2	Cocaine use disorder
F15.1, F15.2	Drug use disorder due to other stimulants
F16.1, F16.2	Drug use disorder due to hallucinogens
F18.1, F18.2	Drug use disorder due to volatile solvents
F19.1, F19.2	Drug use disorder due to multiple drug use and other psychoactive substances

4.2.1.3 Covariates

All covariates were measured at baseline.

Place of upbringing (before age 18) with three response categories: Stockholm County, another part of Sweden, or abroad. *Country of birth* with two response categories: Sweden or abroad.

Adverse childhood circumstances (before age 18 years) were captured using experience of *economic deprivation during childhood* (no; yes, slight and/or for short periods; yes, severe and/or for longer periods) and experience of *serious family tensions during childhood* (no; yes, slight and/or for short periods; yes, severe and/or longer periods).

Socioeconomic position (SEP) was obtained based on self-reported occupation, coded according to Statistics Sweden's Goldthorpe- Erikson Classification Scheme and grouped as: low (unskilled worker, skilled worker), medium (low level non-manual employee), and high (intermediate level non-manual worker, high level non-manual worker, self-employed worker/professional).

Information on attained *education* (seven response categories collapsed into three categories) grouped as: tertiary; completed post upper secondary education minimum 2 years or university education minimum 3 years, secondary; completed practical or theoretical upper secondary school and primary; completed elementary, primary school.

Alcohol consumption was measured using the AUDIT [93]. Points from the AUDIT questionnaire were summated and used as a continuous variable.

4.2.2 Measures Study 2 (WAG)

4.2.2.1 Predictor

Lifetime cannabis use was assessed using the Composite International Diagnostic Interview – Substance Abuse Module (CIDI-SAM) where participants answered whether they had used any of the drugs included in CIDI-SAM. Those who answered affirmatively to having used cannabis (marijuana, pot grass, hashish, bhang, ganja) were grouped as exposed compared with the non-users.

4.2.2.2 Outcomes

Lifetime diagnosis of depression (major depression or dysthymia) or *anxiety* (agora phobia, social phobia, simple phobia, generalized anxiety disorder, atypical anxiety) were assessed by the trained clinicians post-interviews, using DSM-III- R or DSM-IV (the latter for the youngest cohorts, born 1980 or -93).

4.2.2.3 Covariates

Unsafe upbringing and *troublesome childhood* were dichotomized, from the five response alternatives (ranging from 1 - very safe/trouble-free, to 5 - very unsafe/troublesome) into safe or trouble-free (alternatives 1–2) and unsafe or troublesome (alternatives 3–5) respectively.

Education was dichotomized in two different ways, first by comparing those who completed at least compulsory school (9th grade in the Swedish education system) with those who did not, and second by comparing those who completed at least upper secondary school (12th grade in the Swedish education system) with those who did not. This was done in order to take potential generational differences in school attendance into consideration.

Hazardous alcohol consumption (HAC) was assessed by a quantity-frequency measure. A loading ranging from 0 to 365 was assigned to alcohol frequency during the preceding 12 months, which was multiplied by quantity of standard drinks per average day of consumption during the same period. This was divided by 52 to obtain standard drinks/week, which was dichotomized based on Swedish guidelines for alcohol consumption for women (≥9 standard drinks/week versus < 9 standard drinks/week).

4.2.3 Measures Study 3 and Study 4 (PS)

STUDY 3

Cannabis use disorder (CUD) as a primary diagnosis in either the NPR (in- and outpatient health care) or VAL (primary health care) – wherever the CUD diagnosis was recorded first (i.e., unique records) – between 1990 and 2016. Both ICD-9 and ICD-10 codes were included, specifically 3043, i.e., cannabis dependence from ICD-9 (utilized until 1996 in Sweden), and F12.1 (harmful use of cannabis) and F12.2 (cannabis dependence) from the ICD-10 (used from 1997 and onwards in Sweden).

Birth cohort was based on birth year and categorized into five-year groups, obtained from the TPR.

Disposable family income, estimated annually based on all income sources in the family (salaries, wages, welfare benefits, pensions, etc.), was obtained for each participant upon their inclusion in the study, categorized into quartiles defined as low, lower-middle, upper-middle, and high.

Highest attained educational level was based on number of school years completed and grouped into three categories: primary education (≤ 9 years), secondary education (12 years) and postsecondary education (> 12 years).

Other psychiatric disorders were identified through the NPR and VAL, irrespective of whether the diagnoses were registered as primary or secondary diagnosis. This allowed identification of individuals with CUD and other psychiatric disorders as well as individuals with psychiatric disorders without CUD, without the groups being mutually exclusive. Unique records of each psychiatric diagnosis were used, which meant each individual could have multiple diagnoses included. The diagnoses included were: 1) other substance-related disorders, 2) schizophrenia and other psychotic disorders, 3) mood-related disorders, 4) neurotic and stress-related disorders, 5) personality disorders, and 6) behavioral disorders. The included ICD-codes are specified in the table below (Table 3).

Table 3. Overview of ICD-codes in each diagnostic group.		
	ICD-10	**ICD-9**
Other substance-related disorders	F10, F11, F13, F14, F15, F16, F18, F19	291, 292, 303, 305
Schizophrenia and other psychotic disorders	F20, F21, F22 F23, F24, F25 F28, F29	293, 295, 296, 297, 298, 299
Mood-related disorders	F30, F31, F32, F33, F34, F38, F39	311
Neurotic and stress-related disorders	F40, F41, F42, F43, F44, F45, F48	300, 308, 309
Personality disorders	F60, F61, F62, F63, F68, F69,	301
Behavioral disorders	F90, F91, F92, F93, F94, F98, F99	312

STUDY 4

Measures in Study 4 were similar to those in Study 3, with the following changes and additions:

Disposable family income was measured in the year before the CUD diagnosis.

Highest attained educational level was also measured in the year before CUD diagnosis. Parental education for those younger than 25 years was used instead of the individuals own educational attainment. Unlike in Study 3 – we wanted to capture the exposure of education as a proxy for socioeconomic position, rather than individual accomplishments (which rather was the purpose of the measure in Study 3). Linkage to the parents was obtained from the Multi-Generation Register.

The diagnoses (CUD and other psychiatric disorders) were retrieved only from the NPR, and not VAL. Due to the difference in study period between the third and fourth study, only diagnoses registered with ICD-10 were used, although the same as specified in Table 3 above.

Healthcare provider was used to show where first diagnosis of CUD was registered, with two alternatives (inpatient care or outpatient care).

Severity of cannabis use disorder was used, based on diagnosis (harmful use or dependence).

4.3 STATISTICAL ANALYSES

4.3.1 Differences between groups

Chi-square tests were used in all studies to examine differences between groups, mainly in relation to cannabis use, CUD diagnosis and CUD readmission. For relationships between categorical and continuous variables, sample T-tests (studies 1-4) and ANOVA (Study 1) were used.

4.3.2 Associations and risks

Logistic regression (Study 1 and Study 2)

Logistic regression analyses were used to examine associations between cannabis user and other illicit drug use (in Study 1), and to examine associations between cannabis use and anxiety and depression (in Study 2). Crude and adjusted analyses were performed, and confidence intervals (95%) were calculated for all estimates, in both studies. Analyses were performed in the SAS software, version 9.4. Throughout the results and discussion in this thesis, the term *odds* is, in most cases, substituted with *risk* as the latter is an intuitive term to grasp, as opposed to odds and odds ratio.

Survival analysis (Study 1 and Study 4)

Cox proportional hazards models were used to examine associations between cannabis use and risk of drug use disorders (in Study 1), and to examine associations between different predictors and risk of readmission (in Study 4). The proportionality assumption was tested graphically with Kaplan-Meier curves. Person-time was calculated as days during follow-up in Study 1, from registration date of the questionnaire until censoring (event or end of follow-up December 31st, 2014). Person-time in Study 4 was calculated as age-difference during follow-up (age at start to age at censoring – event, death, end of follow-up December 31st, 2016), since age was the underlying timescale. Crude and adjusted analyses were performed, and confidence intervals (95%) were calculated for all estimates in both studies. Analyses were performed in the SAS software, version 9.4.

In Study 4, an extension to the survival analysis was used – flexible parametric modeling, which allowed modeling of non-proportional hazards and time-varying variables. Analyses were performed in STATA 15.

Additive interaction (Study 2)

The relative excess risk due to interaction (RERI) [94] was used in Study 2, to examine the potential effect that time could have on the associations between cannabis use and anxiety or depression. The method and statistical code from Andersson et. al. (2005), was applied. Two additional measures of interaction were calculated: the attributable proportion and synergy index, available in supplementary material.

4.3.3 Cluster analysis (Study 3)

K-mode is an unsupervised, data-driven cluster analysis [95,96], which was used in Study 3 to explore possible underlying compositions in the population with regard to cannabis use disorder, sociodemographic factors, and psychiatric disorders. The cluster analysis allows this exploration of variable combinations without assessing effects of (and interactions between) specific variables, which was preferable considering the study aim. The Elbow method was used to assess optimal number of clusters prior to commencing the actual clustering [97]. The Elbow method plots different numbers of clusters in relation to the cost function, and the optimal number of clusters is the point where the change of the slope goes from steep to shallow. K-mode clusters individual observations based on a dissimilarity measure, assessed by the total mismatches of variable attributes between two observations (also known as

simple matching). This method is suitable for categorical data and therefore fitting to use in Study 3. First, number of initial modes are chosen which indicate how many clusters will be generated. Second, each observation is allocated to the nearest cluster based on the mode of that observation. Third, the dissimilarity of observations in relation to their modes, is retested and clusters are updated based on potential changes (e.g., one observation might be near a different mode). The third step is repeated until no further changes appear.

4.4 ETHICAL CONSIDERATIONS

The World Medical Association has since its formation aimed to establish and promote high ethical standards and has by way of this pursuit adopted policies and declarations – the well-known Declaration of Helsinki being the most influential document in research ethics concerning human subjects [98]. The declaration highlights different areas (eg., risks and benefits, vulnerable groups, and privacy, to mention a few), and states that all precautionary measures should be taken to protect and safeguard research subjects. It further states that this responsibility lies entirely with the researcher, even though consent has been given by the research subjects. As research rarely (rather never) is harmless, it may only be conducted if anticipated benefits outweigh the risks.

The Swedish Ethical Review Authority assesses and approves the ethical aspects of research projects. In this thesis, ethical approval was obtained for all research projects from which data was utilized, hence all data were collected in accordance with ethical regulations in Sweden. The data sources in this thesis vary (survey, interviews, register linkage) and the ethical considerations follow suit.

For instance, informed consent was obtained either verbally, in writing or by answering the questionnaire for Study 1 and Study 2, however, the requirement for informed consent in Study 3 and Study 4 was waived as data comprised administrative registers and therefore did not require informed consent per se. Since register-based research should be carried out ensuring individual integrity and privacy, data was instead de-identified and pseudonymized which protected the included individuals while enabling register-linkage for research purposes. Nevertheless, the studies utilized personal data and due to the organic approach of register-based research (using secondary data), some individuals may not be aware of the fact that data including their personal information is included in research. Further ensuring protection of privacy and anonymity, the ‘key’ unlocking the connection between individual’s personal identification number and the assigned research identification number was always kept apart from the data I analyzed (including the non-register-based studies). The key remained either at the governmental agencies holding the data (PS) or with the principal investigators for the respective research projects (PART and WAG).

With regard to voluntary participation, participants in the PART study and WAG cohort were informed about this before entering the respective studies. They were also informed about their right to withdrawal. However, this requirement was not considered for individuals included in the PS studies, for reasons specified above, and serves as another example of differences in ethical considerations guiding research.

Importantly, data access to original sets was always restricted to data holders with security clearance and I only obtained data on pre-specified variables, that were documented in relation to research questions and study aims, which were approved by data holders.

In times where cyber security is ever relevant, data storage and management must be considered. All data used in this thesis was stored securely in dedicated KI-servers and all work was conducted directly with the secured KI-server, no data was stored locally. The COVID-19 pandemic affected our ability to work in the office and as a solution, VPN (Virtual Private Network) was used as the new, normal way of work. VPN establishes a secure connection to the KI-network and servers, essentially equated to working on-site and although this technically allows for free movement and possibility to work from most corners of the world, data was never brought outside the vicinities of Sweden (and in actuality; Stockholm) – in accordance with the ethical permits being granted and therefore applicable solely in Sweden. During 2018/19 the GDPR (General Data Protection Regulation) law was implemented in Sweden and affected data storage and management of personal, sensitive data. This change was cause for timely discussions within several arenas in society, and of course differences in opinion for example about the *to be or not to be* free to access data within Stockholm, Sweden, or even the European Union. Although the GDPR updates coupled with the pandemic and the imposed travel restrictions (as measures to mitigate the pandemic) limited our freedom of movement, it was never an option to access the data used in this thesis, outside of Sweden due to the ethical dilemmas implied by doing so.

Furthermore, we focus on a somewhat vulnerable group of individuals, often with combined mental health problems whom we aimed to understand better than what was known before. As stipulated in the Declaration of Helsinki, medical research on vulnerable groups is *"justified if the research is responsive to the health needs or priorities of this group"* [99] – which we believe it is, as we have highlighted their related healthcare needs. Additionally, our research has been cost-effective and efficient as it was based on already collected data, especially the registered-based studies where the administrative data would have been collected irrespective of our research projects. However, it is particularly important to note that the individuals we do not reach in our studies are often a more vulnerable group (e.g., refugees, undocumented individuals, homeless individuals or those outside the social security system) and our research findings may not be generalized to them.

Lastly, our timely research generated findings which may be valuable for healthcare planners and policymakers as they plan and prepare the healthcare (system), especially emphasizing complex mental health problems. It is of ethical importance to conduct as sound studies as possible, with motivated designs, where the generated results may impact individuals in a helpful way. We have attempted to do so, while exhausting the data in relation to study aims (especially relevant for Study 1 and Study 2) as well as carefully considering the essential variables and feasible approaches to our studies. Still, improvements can be made, and much work remains in the field of cannabis use, but the contributions of this thesis to the field are nonetheless a step towards increased understanding.

5 SUMMARY OF RESULTS

The main results from each study are summarized below, more details are found in the respective articles included in the thesis.

STUDY 1 Examination of the association between cannabis use and subsequent other illicit drug use, and drug use disorders (harmful use and dependence)

In our full sample from the PART study, almost eighteen percent (17.9%) reported lifetime use of cannabis (Study 1, Table 2). Cannabis users were younger than non-users and there were more males reporting cannabis use than women – for both ever use and recent use. Family tensions during childhood was more common among recent users and ever user than for never users. Alcohol consumption was higher among cannabis users and highest for recent users.

Cannabis users had elevated risks of other illicit drug use, where recent cannabis users demonstrated higher risks than lifetime users (Study 1, Table 3). Adjusting for age and alcohol consumption reduced the risk of other illicit drug use the most, for both groups of cannabis users. The fully adjusted estimate was attenuated but still showed significantly high risks of other illicit drug use at follow-up for both ever users and recent users (OR = 4.42, 2.91-6.70 95% CI, and OR = 9.66, 4.91-19.03 95% CI respectively).

Among lifetime cannabis users, there was no independent risk increase of drug use disorders during follow-up (Manuscript 1, Table 4). Individuals with lifetime use of illicit drugs, either including or excluding cannabis, did however show elevated risks of drug use disorders. Adjusting for serious family tension during childhood, and alcohol consumption respectively, reduced the risk of drug use disorders the most, for individuals reporting illicit drug use irrespective of also using cannabis or not. The fully adjusted results were attenuated but nonetheless showed elevated risks for drug use disorders at follow-up for individuals reporting other illicit drug both including and excluding cannabis use (HR = 7.27, 3.85-13.75 95% CI and HR = 8.12, 3.41-19.33 95% CI respectively).

STUDY 2 Examination of the association between cannabis use and anxiety and depression; finding out whether any such association changes over time

In our full sample from the WAG cohort, almost twenty-four percent (23.8%) reported cannabis use and between the three cohorts, cannabis use was highest in the youngest (32.6%, Study 2, Table 1). Prevalence of anxiety was under ten percent in the oldest (7.9%) and second oldest (9.9%) cohort, and more than twice as high in the youngest cohort (24.5%). However, prevalence of depression was similar across cohorts at around twenty percent, the youngest cohort displayed only slightly higher prevalence (25.2%). In all three cohorts,

unsafe upbringing and troublesome childhood was more common among cannabis users compared to non-users.

In the oldest cohort, cannabis use was associated with anxiety (Study 2, Table 2). The association persisted after adjustment of unsafe upbringing and troublesome childhood although attenuated (OR = 4.70, 1.61-13.72 95% CI). In the second oldest cohort, there was no association with anxiety and the association between cannabis use and depression was fully attenuated after adjustment. In the youngest cohort, cannabis use was associated with both anxiety and depression, and the associations were attenuated by all covariate adjustment. In the fully adjusted models, the risk of anxiety was lower than that of depression (OR = 1.74, 1.05-2.88 95% CI and OR = 2.47, 1.51-4.06) respectively).

The relative excess risk due to interaction (between cannabis use and time period of cannabis use) was significant for the association between cannabis use and depression, even after adjustment for unsafe upbringing and troublesome childhood (Study 2, Table 3). The youngest cohort had an increased risk of depression compared to the older cohorts, both when compared to them separately (oldest: RERI = 1.41, 0.25-2.56 95% CI and youngest: 1.73, 0.42-3.05 95% CI) and when the youngest cohort was compared to the older cohorts grouped together (RERI = 1.61, 0.42-2.80 95% CI).

STUDY 3 Exploration of individuals with cannabis use disorder in Sweden 1990-2016; characterizing sex, birthyear, socioeconomic factors and psychiatric disorders

In our analytical sample of over 3.3 million individuals born between 1970 and 2000, fourteen thousand individuals had a CUD diagnosis (0.42%). Number of registered CUD diagnoses per 100 000 increased over time, especially among those born 1990 and later (Study 3, Figure 1).

Individuals with CUD were mainly young men (Study 3, Table 1). The vast majority of those diagnosed with a CUD also had another psychiatric disorder (80.1%) compared to those without a CUD where only a fifth had another psychiatric diagnosis (19.1%). Among individuals with CUD, the most common other psychiatric disorder was substance-related disorders, whereas neurotic and stress-related disorders were the most common among individuals without CUD.

We found four distinct clusters (Study 3, Table 2 and Figures 2a-2b), two of which included larger proportions of individuals with CUD (clusters 1 and 4). Cluster 1 had the highest proportion of CUD and mainly comprised young men, with low income and high proportion of substance-related disorders. Cluster 4 had the second highest proportion of CUD and mainly comprised young women, with high income and the highest proportion of behavioral disorders. Clusters 2 and 3 comprised mainly women with mood-related disorders and

neurotic and stress-related. Individuals in cluster 2 were somewhat older than those in cluster 3 and belonged mainly to the lower-middle income group compared to those in cluster 3, who rather belonged to the upper-middle income group.

STUDY 4 Examination of readmission among individuals with cannabis use disorder; characterization and risk estimation of readmission

In our analytical sample of more than twelve thousand individuals with CUD, the vast majority of CUD diagnoses were identified in the outpatient care (~80%) and harmful use of cannabis was more common than cannabis dependence (55.3%). Over twenty percent (23.1%) readmitted during follow-up (Study 4, Table 1). There was no difference in the proportion of readmission between men and women, but differences within educational groups and income levels revealed that readmission was more common among those with low education and low income.

In the univariate analysis, men did not show an increased risk of readmission compared to women (Study 4, Table 2). Individuals with primary education and low income, respectively, had increased risks of readmission compared to those with higher levels, as did individuals with cannabis dependence compared to those diagnosed with harmful use. Having a psychiatric disorder at baseline, other than CUD, increased the risk of readmission, and the highest was observed for schizophrenic and psychotic disorders, personality disorders, and mood-related disorders.

Adjusting for socioeconomic factors, severity of CUD and healthcare provider marginally attenuated the estimates. However, including adjustment of other psychiatric disorders, the risk of readmission for men was somewhat increased compared to women (HR = 1.11, 1.01-1.22 95% CI). After full adjustment, the risks of readmission for individuals with schizophrenic and psychotic disorders, personality disorder, and mood-related disorders persisted although attenuated ($HR_{.}$ = 1.54, 1.29-1.64 95% CI, $HR_{.}$ = 1.27, 1.05-1.54 95% CI, HR = 1.27, 1.12-1.45 95% CI, respectively).

Sensitivity analyses testing different definitions of readmission, based on time since first CUD diagnosis, revealed minor changes in the risk of readmission (Study 4, supplementary Table S4). Decreasing time since first diagnosis and instead measuring readmission at least three months after first diagnosis modestly increased the risks of readmission. When increasing the time to nine and twelve months the estimates were somewhat lower.

The risk of readmission varied by age and was higher among individuals aged 18-35 years old (Study 4, Figures 1-3).

6 DISCUSSION

The overarching aim of this thesis was to increase the understanding of cannabis use, other illicit drug use and drug-related morbidity, by using a variety of Swedish population-based data. Influence of correlates and development over time was in particular focus, as well as findings of clinical relevance or important for healthcare.

First, we found a clear risk increase among cannabis users, of subsequently using other illicit drugs. The risk was higher for recent users compared to lifetime users. We also found that lifetime users of cannabis and no other illicit drugs, did not have an increased risk of drug use disorders, compared to lifetime users of other illicit drugs – whether or not cannabis was included. Serious family tensions during childhood and alcohol use attenuated the associations.

Second, we observed that cannabis use was associated with anxiety and depression among the youngest women. We also found that cannabis use in recent years was associated with depression, unlike cannabis use during earlier years.

Highlights

- Cannabis use did not independently increase the risk of drug use disorders.
- The period of cannabis use seemed to be associated with having a diagnosis of depression.
- Individuals with a registered CUD diagnosis within the healthcare in Sweden increased over time, especially among individuals born 1990 and later.
- Common CUD-related factors were young age, low education level, other substance-related disorders among men, and behavioral disorders among women.
- Over twenty percent readmitted to care due to a CUD diagnosis.
- Risk of CUD readmission was highest among individuals with schizophrenic and psychotic disorders, mood-related disorders, and personality disorders.
- Young individuals (18-35 years) had highest risk of CUD readmission.

Third, we identified clusters in the total population with regard to sociodemographic factors and psychiatric disorders. Two clusters were characterized by slightly higher proportions of individuals with CUD compared to the remaining clusters; one cluster comprised young men with low education and income, and high proportions of other substance-related disorders, another cluster comprised young women with low education, high income, and high proportion of behavioral disorders.

Fourth, we found that most CUD visits took place in the outpatient care during the first two months from initial CUD diagnosis, irrespective of CUD severity. We also found that over twenty percent were readmitted to care during follow-up and that the risk was highest among individuals with only primary education, schizophrenic and psychotic disorders, mood-related disorders, and personality disorders.

6.1 FINDINGS IN A BROADER CONTEXT

6.1.1 Cannabis and other drugs

Cannabis use related to other illicit drugs has been well researched, yet previous studies show somewhat mixed results regarding the influence of cannabis use itself on subsequent drug use

disorders, which have mainly been attributed to differences in measurements and study design [13].

The results from Study 1 are partially in line with previous research, where cannabis use increased the risk of other illicit drug use at follow-up [37,100], but they are in contrast with previous findings with regard to risk of drug use disorders during follow-up [101]. This is likely due to differences in measurement, as mentioned in the review above [13], where our exposure is measured at one time point and only captures lifetime use. Furthermore, the outcome measure of drug use disorder captured only the severe cases as we used specialized healthcare data, consequently omitting potential cases registered elsewhere (primary healthcare, social services, treatment/rehab clinics) or those not seeking and/or receiving care [102].

Alcohol use and alcohol problems partly explained the associations between cannabis use and both other illicit drug use and drug use disorders. This is in line with previous studies [e.g., 6] which also suggest alcohol to be one of the first steps in the invariant sequence of drug use [41] and has also been corroborated in a Swedish study [104]. Unexpectedly, factors such as family tension during childhood, education, and socioeconomic position did not affect the associations to any great extent as previous studies have shown [13,105]. However, our findings are in line with a previous study on the same material [56] and elsewhere [106,107].

The somewhat divergent results between our study and others, may be due to country-, culture-, and context-specific factors that most likely influence the associations between cannabis use and other illicit drugs [41], and may be affected by environmental factors that we do not assess.

6.1.2 Associations with psychiatric comorbidity

Associations between cannabis use and several mental health problems have been documented in many studies, from self-reported symptoms to disorders assessed with clinical diagnoses. Uncertainty remains due to the difficulty of assessing these associations in terms of causality and the nearly countless interactions.

Suggested explanations for the association between cannabis use and depression in later years are, for instance, an increased THC concentration, or a decreased risk perception [108]. Unfortunately, we are unable to attribute the association to any of the proposed explanations, or even other factors such as environment or lifestyle. Higher THC concentration has been shown to increase the risk of psychotic disorders [26], and anxiety and depressive symptoms [109]. This increase is in turn suggested as an explanation for temporal changes in associations, for example between cannabis use and depression [108]. However, we lack specific information about the cannabis our participants use, although a safe assumption would be that it is similar to that used in the rest of Europe, since most cannabis in Sweden is imported [110]. Importantly, the prevalence of depression was higher than that of anxiety and perhaps this is the most plausible explanation to us identifying an association. In either case,

given that depression is associated with, for example, suicidal ideation and attempt [24,111], this is an important finding to expand on.

Regarding CUD, which is more common among men [63,64] and younger individuals [63,67], common psychiatric disorders present in our study population (Study 3) were slightly different depending on sex, although mood and anxiety disorders were common and corresponding to prior research [61,62,82]. We observed a similar proportion of individuals with CUD also having other psychiatric disorders similar to a previous study [112].

High proportion of CUD was observed among younger individuals, irrespective of sex and was observed in two distinct clusters. Other substance-related disorders were especially common among men, which is not a novelty, and among women we observed a high proportion of behavioral disorders, which was slightly surprising. Potential explanations of the similarities and differences are many, and may include increased vulnerability and/or sensitivity among young individuals compared to older which may increase the risk of developing CUD [26,63,67,68], or higher consumption levels [113], or more potent cannabis [114] – or a combination of all. Furthermore, in younger populations, mood-related and neurotic and stress-related disorders may be important driving factors for CUD, or vice versa. This might explain the similar proportions of the aforementioned disorders, as they are related to age of onset [81,115–118].

In short

- Complex relationships require sophisticated study designs.
- THC concentration may affect associations with mental health problems.
- Common mental health problems among cannabis users are other substance-related, mood-related, behavioral, and personality disorders
- There seem to be sex differences in healthcare profiles.
- Young individuals seem to be more affected by health problems related to cannabis use.
- Age differences in health consequences may be related to consumption patterns among younger individuals.

Examining the associations between baseline psychiatric disorders and the risk of readmission during follow-up may only be part of the story, as it is possible that individuals developed one of the included disorders during follow-up – inferring underestimation of their impact on the risk of CUD readmission. The significance of comorbidity, has effects on treatment outcomes and has been highlighted in a recent commissioned report in Sweden [119].

6.1.3 Cannabis use disorder in healthcare

The clear increase in CUD diagnosis from 2001 and onwards, among those born 1995 and later is cause for concern. The individuals were between 11 and 20 years during the mentioned time period, the majority received their diagnosis at 16-18 years old (data not shown), which is a young age. However, taking onset of CUD into account among young cannabis users (which is often within the first year of cannabis use) [115], an increase during that time period is expected. Furthermore, a slight increase in frequent cannabis use among individuals aged 16-19 years has been observed over time [120].

Our observation of different healthcare profiles, of women having higher proportions of mood-related, neurotic, and behavioral disorders while men have higher proportions of substance-related disorders, point to the relevance of screening for cannabis use and CUD in several parts of psychiatric care. Especially women, who often show up in non-substance-related care and also may be dealing with a variety of different mental health problems [121]. However, in keeping with previous studies, we found no difference in risk of readmission between men and women [69,83], despite the differences in healthcare profile – which in itself and irrespective of sex has been shown to increase the risk of readmission [83], in line with our findings. We also observed elevated risks of readmission among those with low income or education, which is similar to previous studies [69,83]. While those with cannabis dependence understandably had higher risk of readmission, healthcare provider did not seem to affect the risk of readmission. We cannot explain this, however a possible explanation may be the somewhat complicated Swedish model for addiction care and treatment, which certainly has regional differences as well as it introduces uncertainty or unclarity regarding responsibilities between primary healthcare, specialized healthcare, and social services.

The risk increase of readmission among young individuals was expected, since most individuals diagnosed with CUD are young, as previous studies have shown [e.g., 2,4]. In Sweden, most individuals receiving care for cannabis-related diagnoses are 15–29 years, and the proportion of individuals aged 30–49 years who receive such care has more than doubled during the past ten years [73]. Further, the proportion of young individuals seeking psychiatric care have increased especially since 2010 [122], which may partially explain the risk increase among younger individuals.

Similar to studies on the course of substance use disorders in general [70], most of the prior studies on CUD have mainly focused on remission rather than on relapse or readmission [71,123]. Our available data lacked information about the individuals between visits, on the type of treatment they received and on their cannabis use (e.g., dose, frequency, type), which did not enable us to assess remission or relapse. As such, despite our results of 77% non-readmission, we cannot make any statements about potential remission. We also observed 15% reappearing in healthcare due to other psychiatric disorders, still meaning approximately 40% did not readmit to specialized healthcare (in- or outpatient care) at all during follow-up of fifteen years. It is likely that some instead appeared in primary healthcare, treatment or rehab clinics, came in contact with social services (disregarding initiating party), or that some indeed remitted. While we are able to identify a group with frequent healthcare utilization and complex healthcare needs, we know less about those not readmitted, particularly those not in our registers.

Additionally, data from social services in recent years also indicate an increase in individuals reporting cannabis as their main substance use problem [73]. However, the lack of detailed information about individuals in substance use treatment, makes it is difficult to assess or evaluate their care, treatment, and course of development. Thorough information about the affected individual's consumption levels and patterns, symptoms (craving, withdrawal), possible remission and relapse, is of great importance especially since substance use disorders are cyclical [80].

6.2 METHODOLOGICAL CONSIDERATIONS

The novelty of this thesis, presenting comprehensive research on cannabis users in Sweden – an understudied group – is a clear strength. The research included here was conducted with a wide range of data sources aiming to increase the understanding of these individuals and their potential development over time, with regards to other illicit drugs and drug-related morbidity including drug dependence. This was done efficiently by utilizing already collected data, which also permitted longitudinal study designs. Another strength is that data in all four studies included women. The studies were general population-based (Study 1 and 2) and total population-based (Study 3 and 4), which increases generalizability. Still, as no study is flawless, some limitations are relevant to mention.

Two studies in this thesis were entirely register-based (Study 3 and 4), and the utilized patient registers have been shown to have generally high quality (high coverage and validated for several diagnoses) [86,124]. In general, the registers are sensitive in that they accurately identify disease, but not specific since they are not designed to have the ability to accurately classify non-disease. This means that individuals that receive care in primary healthcare or social services, for any of the psychiatric disorders examined in this thesis, are not represented. The same is true for those who are in fact undiagnosed. VAL was utilized in Study 3, which has better coverage of psychiatric disorders, however it only includes the population in Stockholm and therefore affects the representativeness. We used first CUD diagnosis and ensured no overlap between where the diagnoses were registered, which perhaps mitigated the effects to some extent. Still, this approach can imply that individuals identified through VAL had less severe diagnoses, and/or that they were diagnosed earlier than those identified through the NPR. We were interested in an overall picture of psychiatric comorbidity/multimorbidity, and therefore chose to use a comprehensive approach. In Study 4, we instead focused on specialized care and excluded the VAL register as we aimed to look at multiple visits over time. Including VAL would have introduced more bias, because only a subset of the population would have had an additional (high coverage and quality) source of healthcare information. An additional factor affecting representativeness is that we cover individuals having sought care or been required to receive care, and thus does not represent the complete magnitude of the problem. Consequently, the results are indicative of healthcare utilization, which is further affected by socioeconomic position [125], and may have led to decreased representativeness of individuals with low socioeconomic position. Therefore, our results may not be generalizable to the broader group of individuals with CUD.

Study 1 and 2 both suffered from attrition, which have been analyzed elsewhere [126,127]. In short, participants in Study 1 were more often female, had high income and education level. In Study 2, initial findings showed no difference between non-responders and participants, however uncertainty remains for the later years [128]. The two-stage design (Study 2) was used to oversample a subgroup of women with alcohol-related problems and the data was then re-weighted to fit the distribution in the target population, which can be used for more efficient sampling while allowing inference to be drawn to the target population [129]. We still prompt caution in terms of generalizability, also due to the restriction to women – even though the inverse has provided generalized evidence [104,130,131]. Nevertheless, sex differences in patterns of cannabis consumption [132] and rates of depression (and anxiety) [e.g., 79] exist and are important to acknowledge when interpreting the results.

Crude measurements of cannabis use (self-reported and lifetime use) affected our study designs and ability to carry out more detailed analyses (Study 1 and 2). This in turn limits our conclusions to be either broad or prudent, or both. Generally, the lack of a quantifiable measure of cannabis use, similar to that of alcohol (grams of ethanol), continues to hamper research [133]. Measuring drug use disorders excluding CUD (outcome in Study 1), it is perhaps self-evident that individuals reporting other illicit drug use will have much higher risks of the outcome. But, here our aim was primarily to assess the impact that cannabis use might (independently) have on the risk of drug use disorders, which we based on the state of previous research [41,57], since the obvious pathway from other illicit drug use at baseline to drug use disorders due to illicit drugs excluding CUD was not of primary interest. Study 1 may have suffered from misclassification regarding inconsistency in reporting illicit drug use between baseline and follow-up [134], however we checked the proportion and it was approximately the same between the two measurement points, also corresponding to national prevalence [135].

In Study 3 we covered a wider study period compared to Study 4, and thus included ICD-9 codes in addition to ICD-10. This implied some differences in the disease classification schemes and may have influenced the number of cases we captured; for instance, ICD-9 does not include harmful use of cannabis but only cannabis dependence, which meant that we may have identified more cases once ICD-10 was implemented – in turn reflective of late diagnosis. Additionally, better assessment of diagnosis and better register coverage in later years may be reason for the improved data quality. Importantly, clinical practice patterns (i.e., how clinicians assess patients and register diagnoses) are essential as they determine the data available in the registers. Unfortunately, we do not have insight on this and can only be aware of this potential source of bias. Decreased enacted stigma regarding CUD through knowledge and awareness may have led to less felt stigma, which would influence care-seeking behavior. Identifying subgroups with different healthcare needs with the cluster analysis (Study 3) [136–138] was of value, however it may be improved by using less comprehensive or general variables and rather explore more detailed variable definitions, or further developing the cluster analysis by stratifying the clustering process and investigating the clusters beyond the current scope.

The assumption in Study 2 about THC-levels in the cannabis consumed in Sweden may be questioned, although data on confiscated cannabis in Sweden is similar to that of other countries Europe, including Denmark which is a source of import (smuggling) [21,22,110]. Furthermore, our conclusions are rather modest, and we do not in fact attribute the observed interaction to the general THC-increase even though it is plausible. The inability to disentangle the period and cohort effects in Study 2 is a limitation. Even though some findings may be indicative of either (or both) period and cohort effects, the findings are rather hypothesis generating than informative about age-, period-, or cohort effects in relation to cannabis use and depression or anxiety. The use of cross-sectional data gives rise to potential reverse causation; however, our focus was to examine differences across time periods, and not longitudinal or causal associations.

Finally, our operationalization of readmission (Study 4) can be questioned, even though sensitivity analyses of readmission at three, nine, and twelve months after first CUD showed minimal changes in risk of readmission. The initial aim was to capture relapse; however, we could not reliably and validly operationalize a measure based on the data available.

Therefore, our measure of readmission is based on assumptions that may not hold, and as such may be subject to scrutiny. However, our conclusions are in line with what was de facto measured and not what was intended (or rather, anticipated) to be measured. Nonetheless, without a coherent definition or operationalization of readmission and relapse, research in this field will continue to be exploratory, complicated, and likely inconclusive – rendering implications for treatment and prevention unspecific and uncertain [139].

7 CONCLUSIONS

Based on the results from this thesis, the following conclusions are drawn:

Lifetime use of cannabis does not independently increase the risk of drug use disorders, although it can significantly increase the risk of other illicit drug use – which in turn increases the risk of drug use disorders.

Cannabis use is associated with anxiety and depression. Cannabis use in recent years seems to be associated with depression, which may potentially be due to an increased potency of cannabis.

Registered CUD diagnoses in Swedish healthcare have increased over time. It may be because of decreased stigma, increased screening and diagnosis of, and/or treatment-seeking for mental health in general. The expansion of diagnostic criteria (to also include harmful use in ICD-10) likely plays an important role in the increase.

Women who use cannabis or are diagnosed with CUD may be overlooked, whereby attention should be directed toward them in order to ensure that suitable treatment and care is provided.

Individuals with CUD have complex healthcare needs. Subgroups of individuals with CUD are identifiable, where young individuals are especially exposed – healthcare systems need to be prepared to meet their needs.

Individuals in their thirties and younger show higher risk of readmission and merit more attention, especially when also considering their overrepresentation among individuals with CUD.

Individuals with CUD have frequent healthcare visits during the first two months, which are later phased out. Over twenty percent were readmitted to care for another CUD diagnosis during a 15-year follow-up period. Individuals with primary education, and those with schizophrenia and psychotic disorders, mood-related disorders or personality disorders had the highest risk of readmission.

8 IMPLICATIONS & FUTURE DIRECTIONS

8.1 IMPLICATIONS

Our findings have clinical relevance, which mainly pertain to healthcare planning related to individuals with a CUD and the reiteration of the important psychiatric complexity.

Importantly, the present findings are not to be extrapolated to inform on questions of decriminalization and legalization of cannabis use as the findings concern cannabis user's health and do not, for instance, incorporate comprehensive societal or social aspects. Nonetheless, considering the interconnectedness between different psychiatric health problems and substance use, it would be valuable to look further into areas of improvement with the current drug policy – towards a clearer health and rehabilitation focus. As such, these findings may be used as grounds for underpinning potentially revised drug and healthcare policies aiming to improve health.

The high comorbidity/multimorbidity observed in this thesis is cause for concern and shows a close association between cannabis use, other drug use and mental health problems, irrespective of causal direction. The Swedish model for addiction care is divided between social services on a municipality level and healthcare system on a regional level [140–142], whereby the social services are responsible for most of the addiction care and the healthcare side provides the necessary treatments and care measures (often after approval by social services and/or legal authorities). This has been criticized as it complicates interventions for what, in today's paradigm, indeed is a medical condition [141]. It is important to offer psychiatric care and treatment irrespective of substance use (disorder) is present or not – and vice versa, and thus not refuse or turn away patients in need of care. Improvements to the healthcare system may perhaps include transferring the main responsibility to the healthcare sector, and better integration between psychiatric care in general and addiction care and treatment, in order to avoid patients slipping through the cracks between the different care providers. Although treating patients with both substance use disorders and other psychiatric disorders is a complex matter, an integrated approach emphasizing collaboration might tackle some of the current difficulties.

Our observations indicate an importance to not overlook women in psychiatric care, with regards to potential cannabis use. Although the proportion of women with CUD is considerably lower than that of men, we did not find a sex difference in the risk of readmission, whereby it seems relevant to refrain from neglecting the potential presence of CUD among women. Considering the overrepresentation of women with mental health problems, other areas within psychiatric care may well pay attention to possible co-occurring cannabis and/or substance use, as well as their respective disorders.

8.2 FUTURE DIRECTIONS

Rich data is cause for great idea generation and not all could be covered in this thesis. We covered what we intended, in some cases on an introductory level, and all that awaits is encouraging and raises curiosity. In a dynamic research field, in times with great

technological advancement, and legislative changes towards lenient drug policies, many opportunities present themselves and thus, as the nature of research, much work remains.

Our findings generate questions for future studies to consider looking into, for example, how does cannabis potency affect risk of anxiety and depression, and is there a dose-response relationship? What is the relationship between cannabis use, CUD, and somatic disorders [e.g., 141]? What other subgroups may exist in relation to substance use disorders and other psychiatric disorders? If variables are grouped differently (e.g., sex-stratified, and/or with psychiatric disorders grouped less rough or assessed individually), what subgroups can be identified? Important aspects to examine further and clarify are accordingly those regarding psychiatric disorders in relation to cannabis use and CUD. This may relate to establishing causality, assessing presence of disorders prior to cannabis use and/or risks of developing certain disorders following cannabis use.

Other aspects of improvement are the crude measurements, be they of unspecific measurements of cannabis use, too general or comprehensive disease categories, or (outcome) measures without validated operationalization such as readmission – which all pose as impediments, as they limit the ability to illustrate potential nuances of cannabis use and potential health effects. Improving information on the specific care patients in healthcare receive, would further enable more detailed research on CUD care and treatment, possibly even provide opportunity for evaluation – highly relevant considering the increase in CUD prevalence and treatment-seeking [73,80,144,145].

Additionally, considering the sex differences related to CUD, a deep diving into the health of women who use cannabis would be of interest, for two reasons in particular; first, significant research on cannabis use among men have been frequent in Sweden [e.g., 129,143,144], and second, a similar focus on cannabis use among women would be valuable to understand if women have specific health(care) needs that may need to be tailored.

Also, continued research aiming to map the endocannabinoid system and the mechanism of cannabis dependence would be of great value. Identifying the mechanisms behind the stages of harmful cannabis use and cannabis dependence would improve our understanding of how this psychoactive substance affects our neurobiology, potentially enabling better targeted (pharmacological) treatment. It may also be interesting to explore the potential of incorporating and developing epigenetic approaches in cannabis-related research.

Lastly, this thesis answers some questions although many remain unanswered, in spite of the societal and public health interest in cannabis. Considering the need for more knowledge, it is important to allow for research to be conducted in due time, so to inform decision-making processes [148,149].

9 ACKNOWLEDGEMENTS

As someone who dreaded flipping through doctoral theses during my undergraduate education, writing this section of my own thesis feels surreal. Needless to say, many have contributed to this journey, and I would like to take this opportunity to express my gratitude and appreciation.

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10 REFERENCES

1. Pacher P, Bátkai S, Kunos G. The endocannabinoid system as an emerging target of pharmacotherapy [Internet]. Vol. 58, Pharmacological Reviews. 2006 [cited 2021 Sep 8]. p. 389–462. Available from: http://pharmrev.aspetjournals.org.

2. UNODC - United Nations Office on Drugs and Crime. World drug report 2. 2018.

3. Ransing R, Antonio P, Rosa D, Pereira-sanchez V, Jibril IM, Jerotic S, et al. perspectives. 2021.

4. Dellazizzo L, Potvin S, Giguère S, Dumais A. Evidence on the acute and residual neurocognitive effects of cannabis use in adolescents and adults: a systematic meta-review of meta-analyses. Addiction [Internet]. 2022 Jan 19 [cited 2022 Jan 30]; Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/add.15764

5. Hall W, Degenhardt L. Prevalence and correlates of cannabis use in developed and developing countries. Curr Opin Psychiatry. 2007;20(4):393–7.

6. Gloss D. An Overview of Products and Bias in Research [Internet]. Vol. 12, Neurotherapeutics. Springer; 2015 [cited 2022 Mar 7]. p. 731–4. Available from: https://link.springer.com/article/10.1007/s13311-015-0370-x

7. Baron EP. Comprehensive review of medicinal marijuana, cannabinoids, and therapeutic implications in medicine and headache: What a long strange trip it's been ... Headache. 2015 Jun 1;55(6):885–916.

8. Warf B. High Points: An Historical Geography of Cannabis. Geogr Rev. 2014;104(4):414–38.

9. Kumar P, Mahato DK, Kamle M, Borah R, Sharma B, Pandhi S, et al. Pharmacological properties, therapeutic potential, and legal status of Cannabis sativa L.: An overview. Phyther Res. 2021;(December 2020):1–20.

10. Collins J. Symposium on drug decriminalization, legalization, and international law: A brief history of cannabis and the drug conventions. AJIL Unbound. 2020;279–84.

11. Connor JP, Stjepanović D, Le Foll B, Hoch E, Budney AJ, Hall WD. Cannabis use and cannabis use disorder. Nat Rev Dis Prim. 2021;7(1):1–24.

12. Lucatch AM, Coles AS, Hill KP, George TP. Cannabis and Mood Disorders. Curr Addict Reports. 2018;5(3):336–45.

13. National Academies of Sciences E and M. The Health Effects of Cannabis and Cannabinoids: The current state of evidence and recommendations for research. [Internet]. Washington DC; 2017. Available from: https://www.nap.edu/catalog/24625

14. Hall W. What has research over the past two decades revealed about the adverse health effects of recreational cannabis use? Addiction [Internet]. 2015 Jan 1 [cited 2019 Sep 24];110(1):19–35. Available from: http://doi.wiley.com/10.1111/add.12703

15. Di Forti M, Quattrone D, Freeman TP, Tripoli G, Gayer-Anderson C, Quigley H, et al. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. The Lancet Psychiatry [Internet]. 2019 [cited 2019 Mar 21];6(5):427–36. Available from: www.thelancet.com/psychiatry

16. Chandra S, Radwan MM, Majumdar CG, Church JC, Freeman TP, ElSohly MA. New trends in cannabis potency in USA and Europe during the last decade (2008–2017). Eur Arch Psychiatry Clin Neurosci [Internet]. 2019 Feb 1 [cited 2020 Mar 4];269(1):5–15. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30671616

17. Smart R, Caulkins JP, Kilmer B, Davenport S, Midgette G. Variation in cannabis potency and prices in a newly legal market: evidence from 30 million cannabis sales in Washington state. Addiction. 2017;112(12):2167–77.

18. ElSohly MA, Mehmedic Z, Foster S, Gon C, Chandra S, Church JC. Changes in cannabis potency over the last 2 decades (1995-2014): Analysis of current data in the United States. Biol Psychiatry. 2016;79(7):613–9.

19. Slade D, Mehmedic Z, Chandra S, ElSohly M. 4. Is cannabis becoming more potent? In: Marijuana and Madness: Second Edition [Internet]. 2011 [cited 2020 Mar 5]. p. 35–54. Available from: https://doi.org/10.1017/CBO9780511706080.005

20. Health Canada. A Framework for the Legalization and Regulation of Cannabis in Canada: The Final Report of the Task Force on Cannabis Legalization and Regulation [Internet]. Drug Testing and Analysis. 2016 [cited 2020 May 12]. Available from: https://www.canada.ca/content/dam/hc-sc/healthy-canadians/migration/task-force-marijuana-groupe-etude/framework-cadre/alt/framework-cadre-eng.pdf%0Ahttp://doi.wiley.com/10.1002/dta.1839

21. Thomsen KR, Lindholst C, Thylstrup B, Kvamme S, Reitzel LA, Worm-Leonhard M, et al. Changes in the composition of cannabis from 2000-2017 in Denmark: Analysis of confiscated samples of cannabis resin. Exp Clin Psychopharmacol. 2019 Aug 1;27(4):402–11.

22. Freeman TP, Groshkova T, Cunningham A, Sedefov R, Griffiths P, Lynskey MT. Increasing potency and price of cannabis in Europe, 2006–16. Addiction. 2019 Jun 1;114(6):1015–23.

23. Freeman TP, Van Der Pol P, Kuijpers W, Wisselink J, Das RK, Rigter S, et al. Changes in cannabis potency and first-time admissions to drug treatment: A 16-year study in the Netherlands. Psychol Med. 2018 Oct 1;48(14):2346–52.

24. Gobbi G, Atkin T, Zytynski T, Wang S, Askari S, Boruff J, et al. Association of Cannabis Use in Adolescence and Risk of Depression, Anxiety, and Suicidality in Young Adulthood: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2019;76(4):426–34.

25. Sideli L, Quigley H, La Cascia C, Murray RM. Cannabis Use and the Risk for Psychosis and Affective Disorders [Internet]. Vol. 16, Journal of Dual Diagnosis. 2020 [cited 2020 Mar 6]. p. 22–42. Available from: https://www.tandfonline.com/action/journalInformation?journalCode=wjdd20

26. Wilson J, Freeman TP, Mackie CJ. Effects of increasing cannabis potency on adolescent health. Lancet Child Adolesc Heal [Internet]. 2019;3(2):121–8. Available from: http://dx.doi.org/10.1016/S2352-4642(18)30342-0

27. UNODC - United Nations Office on Drugs and Crime. World Drug Report (1) 2018. 2018.

28. United Nations Office On Drugs Crime (UNODC). World Drug Report 2021 - Executive summary, Policy implications. United Nations [Internet]. 2021 [cited 2022

Mar 24]; Available from: www.unodc.org/unodc/en/data-and-analysis/wdr2021.html

29. UNODC. World Drug Report 2019 (United [Internet]. 2019 [cited 2020 Jun 5]. Available from: www.unodc.org/wdr2019

30. Rotermann M. Analysis of trends in the prevalence of cannabis use and related metrics in Canada. Heal Reports [Internet]. 2019 Jun 1 [cited 2020 Apr 18];30(6):3–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31216047

31. Health M of. Cannabis Use 2012/13: New Zealand Health Survey. 2012.

32. Australian Institute of Health and Welfare. National Drug Strategy Household Survey 2016: detailed findings. [Internet]. Drug stati. Canberra; AIHW; 2017 [cited 2020 Apr 19]. Available from: www.aihw.gov.au

33. Sweden TPHA of. Public health reporting - cannabis use [Internet]. Available from: https://www.folkhalsomyndigheten.se/folkhalsorapportering-statistik/tolkad-rapportering/folkhalsans-utveckling/resultat/levnadsvanor/cannabisanvandning-i-befolkningen/.

34. Fergusson DM, Boden JM, Horwood LJ. Psychosocial sequelae of cannabis use and implications for policy: findings from the Christchurch Health and Development Study [Internet]. Vol. 50, Social Psychiatry and Psychiatric Epidemiology. Dr. Dietrich Steinkopff Verlag GmbH and Co. KG; 2015 [cited 2020 Apr 18]. p. 1317–26. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26006253

35. Dahlgren G, Whitehead M. The Dahlgren-Whitehead model of health determinants: 30 years on and still chasing rainbows. Public Health. 2021 Oct 1;199:20–4.

36. Danielsson AK, Agardh E, Hemmingsson T, Allebeck P, Falkstedt D. Cannabis use in adolescence and risk of future disability pension: A 39-year longitudinal cohort study. Drug Alcohol Depend [Internet]. 2014;143(1):239–43. Available from: http://dx.doi.org/10.1016/j.drugalcdep.2014.07.038

37. Mayet A, Legleye S, Beck F, Falissard B, Chau N. The Gateway Hypothesis, Common Liability to Addictions or the Route of Administration Model? A Modelling Process Linking the Three Theories. Eur Addict Res. 2016;22:107–17.

38. Kandel D. Stages in adolescent involvement in drug use. Science (80-) [Internet]. 1975;190(4217):912–4. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emcl2&NEWS=N&AN=0976186453

39. Agrawal A, Neale MC, Prescott CA, Kendler KS, Agrawal A, Neale MC, et al. A twin study of early cannabis use and subsequent use and abuse / dependence of other illicit drugs A twin study of early cannabis use and subsequent use and abuse / dependence of other illicit drugs. 2013;(May):1227–37.

40. Hicks BM, Iacono WG, McGue M. Index of the transmissible common liability to addiction: Heritability and prospective associations with substance abuse and related outcomes. Drug Alcohol Depend [Internet]. 2012;123(SUPPL.1):S18–23. Available from: http://dx.doi.org/10.1016/j.drugalcdep.2011.12.017

41. Lynskey MT, Agrawal A. Denise Kandel's classic work on the gateway sequence of drug acquisition. Addiction. 2018;113(10):1927–32.

42. Fergusson DM, Boden JM, Horwood LJ. The developmental antecedents of illicit drug use: Evidence from a 25-year longitudinal study. Drug Alcohol Depend. 2008;96(1–2):165–77.

43. Secades-villa R, Garcia-rodríguez O, Jin CJ, Wang S, Blanco C. Probability and predictors of the cannabis gateway effect : A national study. Int J Drug Policy [Internet]. 2015;26(2):135–42. Available from: http://dx.doi.org/10.1016/j.drugpo.2014.07.011

44. Lynskey M, Heath A, Bucholz K, Slutske W, Madden PAF, Nelson E, et al. Escalation of drug use in early-onset cannabis users vs co-twin controls. J Am Med Assoc [Internet]. 2003;289(4):427–33. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=36119962

45. Lynskey MT, Vink JM, Boomsma DI. Early Onset Cannabis Use and Progression to other Drug Use in a Sample of Dutch Twins. Behav Genet [Internet]. 2006 Mar 10 [cited 2019 Mar 24];36(2):195–200. Available from: http://link.springer.com/10.1007/s10519-005-9023-x

46. Agrawal A, Lynskey MT. Cannabis controversies: how genetics can inform the study of comorbidity. Addiction [Internet]. 2014 Mar;109(3):360–70. Available from: http://doi.wiley.com/10.1111/add.12436

47. Marconi A, Di Forti M, Lewis CM, Murray RM, Vassos E. Meta-Analysis of the association between the level of cannabis use and risk of psychosis. Schizophr Bull. 2016;42(5):1262–9.

48. Harrison C, Fortin M, van den Akker M, Mair F, Calderon-Larranaga A, Boland F, et al. Comorbidity versus multimorbidity: Why it matters. J Multimorbidity Comorbidity [Internet]. 2021 [cited 2022 Mar 14];11:263355652199399. Available from: https://us.sagepub.com/en-us/nam/open-access-at-sage

49. Navickas R, Petric V-K, Feigl AB, Seychell M. Multimorbidity: What do we know? What should we do? J comorbidity [Internet]. 2016 Feb 17 [cited 2022 Mar 14];6(1):4–11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29090166

50. Taylor M, Collin SM, Munafò MR, MacLeod J, Hickman M, Heron J. Patterns of cannabis use during adolescence and their association with harmful substance use behaviour: Findings from a UK birth cohort. J Epidemiol Community Health. 2017;71(8):764–70.

51. Meier MH, Caspi A, Ambler A, Harrington H, Houts R, Keefe RSE, et al. Persistent cannabis users show neuropsychological decline from childhood to midlife. Proc Natl Acad Sci [Internet]. 2012;109(40):E2657–64. Available from: http://www.pnas.org/cgi/doi/10.1073/pnas.1206820109

52. Lev-Ran S, Le Foll B, McKenzie K, George TP, Rehm J. Bipolar disorder and co-occurring cannabis use disorders: Characteristics, co-morbidities and clinical correlates. Psychiatry Res [Internet]. 2013 Oct [cited 2019 Sep 23];209(3):459–65. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0165178112008116

53. Stenbacka M, Allebeck P, Romelsjö A. Initiation into drug abuse: The pathway from being offered drugs to trying cannabis and progression to intravenous drug abuse. Scand J Public Health. 1993;21(1):31–9.

54. Kedzior KK, Laeber LT. A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population- a meta-analysis of 31 studies. BMC Psychiatry. 2014;14(1):1–22.

55. Botsford SL, Yang S, George TP. Cannabis and Cannabinoids in Mood and Anxiety Disorders: Impact on Illness Onset and Course, and Assessment of Therapeutic Potential. Am J Addict [Internet]. 2019 Oct 2 [cited 2019 Oct 17];ajad.12963. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/ajad.12963

56. Danielsson A-K, Lundin A, Agardh E, Allebeck P, Forsell Y. Cannabis use, depression and anxiety: A 3-year prospective population-based study. J Affect Disord. 2016;193:103–8.

57. Blanco C, Hill KP, Hasin DS, Wall MM, Flórez-Salamanca L, Hoertel N, et al. Cannabis use and risk of psychiatric disorders: Prospective evidence from a US national longitudinal study [Internet]. Vol. 317, JAMA - Journal of the American Medical Association. American Medical Association; 2017 [cited 2019 Mar 21]. p. 1070–1. Available from: http://archpsyc.jamanetwork.com/article.aspx?doi=10.1001/jamapsychiatry.2015.3229

58. Van der Pol P, Liebregts N, De Graaf R, Ten Have M, Korf DJ, Van den Brink W, et al. Mental health differences between frequent cannabis users with and without dependence and the general population. Addiction. 2013;108(8):1459–69.

59. Myers B, McLaughlin KA, Wang S, Blanco C, Stein DJ. Associations between childhood adversity, adult stressful life events, and past-year drug use disorders in the National Epidemiological Study of Alcohol and Related Conditions (NESARC). Psychol Addict Behav [Internet]. 2014 Dec [cited 2019 Sep 23];28(4):1117–26. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25134042

60. Greydanus DE, Hawver EK, Greydanus MM, Merrick J. Marijuana: Current Concepts†. Front Public Heal [Internet]. 2013;1(October):1–17. Available from: http://journal.frontiersin.org/article/10.3389/fpubh.2013.00042/abstract

61. Lev-Ran S, Imtiaz S, Rehm J, Le Foll B. Exploring the association between lifetime prevalence of mental illness and transition from substance use to substance use disorders: Results from the National Epidemiologic Survey of Alcohol and Related Conditions (NESARC). Am J Addict. 2013;22(2):93–8.

62. Khan SS, Secades-Villa R, Okuda M, Wang S, Pérez-Fuentes G, Kerridge BT, et al. Gender differences in cannabis use disorders: Results from the National Epidemiologic Survey of Alcohol and Related Conditions. Drug Alcohol Depend [Internet]. 2013 Jun 1 [cited 2020 Mar 29];130(1–3):101–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23182839

63. Hasin DS, Kerridge BT, Saha TD, Huang B, Pickering R, Smith SM, et al. Prevalence and correlates of DSM-5 cannabis use disorder, 2012-2013: Findings from the national epidemiologic survey on alcohol and related conditions-III [Internet]. Vol. 173, American Journal of Psychiatry. American Psychiatric Association; 2016 [cited 2020 Mar 29]. p. 588–99. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26940807

64. Kerridge BT, Pickering R, Chou P, Saha TD, Hasin DS. DSM-5 cannabis use disorder in the National Epidemiologic Survey on Alcohol and Related Conditions-III: Gender-specific profiles. Addict Behav. 2018 Jan 1;76:52–60.

65. World Health Organization. The ICD-10 classification of mental and behavioural disorders: Clinical descriptions and diagnostic guidelins. 1992. 1–267 p.

66. American Psychiatric Association (APA). Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR, fourth ed. Washington, DC.: American Psychiatric Association,; 2000.

67. Wu LT, Zhu H, Mannelli P, Swartz MS. Prevalence and correlates of treatment utilization among adults with cannabis use disorder in the United States. Drug Alcohol Depend. 2017 Aug 1;177:153–62.

68. Han B, Compton WM, Blanco C, Jones CM. Time since first cannabis use and 12-month prevalence of cannabis use disorder among youth and emerging adults in the United States. Addiction [Internet]. 2019 Apr 21 [cited 2019 Apr 15];114(4):698–707. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/add.14511

69. Farmer RF, Kosty DB, Seeley JR, Duncan SC, Lynskey MT, Rohde P, et al. Natural course of cannabis use disorders. Psychol Med [Internet]. 2015 [cited 2019 Dec 19];45(1):63–72. Available from: https://doi.org/10.1017/S003329171400107X

70. Feingold D, Fox J, Rehm J, Lev-Ran S. Natural outcome of cannabis use disorder: A 3-year longitudinal follow-up. Addiction. 2015;110(12):1963–74.

71. Lewer D, Freer J, King E, Larney S, Degenhardt L, Tweed EJ, et al. Frequency of healthcare utilisation by adults who use illicit drugs: a systematic review and meta-analysis. Addiction [Internet]. 2019;add.14892. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/add.14892

72. Kosty DB, Seeley JR, Farmer RF, Stevens JJ, Lewinsohn PM. Trajectories of cannabis use disorder: risk factors, clinical characteristics and outcomes. Addiction [Internet]. 2017 [cited 2019 Apr 15];112(2):279–87. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27515021

73. Socialstyrelsen. Missbruk, substansrelaterade diagnoser och spel om pengar. [Internet]. 2021. Available from: https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/ovrigt/2021-4-7277.pdf

74. Christensen AI, Ekholm O, Gray L, Glümer C, Juel K. What is wrong with non-respondents? Alcohol-, drug- and smoking-related mortality and morbidity in a 12-year follow-up study of respondents and non-respondents in the Danish Health and Morbidity Survey. Addiction. 2015;110(9):1507–14.

75. Lowe DJE, Sasiadek JD, Coles AS, George TP. Cannabis and mental illness: a review. Eur Arch Psychiatry Clin Neurosci [Internet]. 2019 Feb 19 [cited 2019 May 29];269(1):107–20. Available from: http://link.springer.com/10.1007/s00406-018-0970-7

76. Myers B, McLaughlin KA, Wang S, Blanco C, Stein DJ. Associations between childhood adversity, adult stressful life events, and past-year drug use disorders in the National Epidemiological Study of Alcohol and Related Conditions (NESARC). Psychol Addict Behav [Internet]. 2014 Dec [cited 2019 Sep 23];28(4):1117–26. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25134042

77. Marconi A, Forti M Di, Lewis CM, Murray RM, Vassos E. Meta-analysis of the Association Between the Level of Cannabis Use and Risk of Psychosis. Schizophr Bull [Internet]. 2016 [cited 2020 Jan 18];42(5):1262–9. Available from:

https://academic.oup.com/schizophreniabulletin/article-abstract/42/5/1262/2413827

78. Hines LA, Freeman TP, Gage SH, Zammit S, Hickman M, Cannon M, et al. Association of High-Potency Cannabis Use With Mental Health and Substance Use in Adolescence. JAMA psychiatry [Internet]. 2020 May 27 [cited 2020 Jun 14]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/32459328

79. Institute for Health Metrics and Evaluation (IHME). Global burden of Disease, Data Visualizations - GBD Compare [Internet]. Available from: https://vizhub.healthdata.org/gbd-compare/

80. Centre NW. Treatment of cannabis-related problems in the Nordic countries [Internet]. 2019 [cited 2021 Oct 15]. Available from: www.nordicwelfare.org

81. Teesson M, Slade T, Swift W, Mills K, Memedovic S, Mewton L, et al. Prevalence, correlates and comorbidity of DSM-IV cannabis use and cannabis use disorders in Australia. Aust N Z J Psychiatry [Internet]. 2012 [cited 2020 Apr 18];46(12):1182–92. Available from: https://www.researchgate.net/publication/230864580

82. Campbell A, Bailey SR, Hoffman KA, Ponce-Terashima J, Fankhauser K, Marino M, et al. Associations between Psychiatric Disorders and Cannabis-Related Disorders Documented in Electronic Health Records. J Psychoactive Drugs [Internet]. 2020 [cited 2021 May 14];52(3):228–36. Available from: https://www.tandfonline.com/action/journalInformation?journalCode=ujpd20

83. Flórez-Salamanca L, Secades-Villa R, Budney AJ, García-Rodríguez O, Wang S, Blanco C. Probability and predictors of cannabis use disorders relapse: Results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Drug Alcohol Depend [Internet]. 2013;132(1–2):127–33. Available from: http://dx.doi.org/10.1016/j.drugalcdep.2013.01.013

84. Singh JA. Time-trends in hospitalizations with cannabis use disorder: A 17-year U.S. national study. Subst Abus [Internet]. 2021 [cited 2021 Nov 11]; Available from: https://www.tandfonline.com/action/journalInformation?journalCode=wsub20

85. Charilaou P, Agnihotri K, Garcia P, Badheka A, Frenia D, Yegneswaran B. Trends of Cannabis Use Disorder in the Inpatient: 2002 to 2011. Am J Med [Internet]. 2017 Jun 1 [cited 2020 Mar 29];130(6):678-687.e7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28161344

86. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health [Internet]. 2011;11(1):450. Available from: http://www.biomedcentral.com/1471-2458/11/450

87. Spak F, Hällström T. Screening for Alcohol Dependence and Abuse in Women: Description, Validation, and Psychometric Properties of a New Screening Instrument, SWAG, in a Population Study. Alcohol Clin Exp Res. 1996;20(4):35–8.

88. Waern M, Spak F, Sundh V. Suicidal ideation in a female population sample: Relationship with depression, anxiety disorder and alcohol dependence/abuse. Eur Arch Psychiatry Clin Neurosci. 2002;252(2):81–5.

89. Sundin M, Spak F, Spak L, Sundh V, Waern M. Substance use/abuse and suicidal behavior in young adult women: A population-based study. Subst Use Misuse. 2011;46(13):1690–9.

90. Ludvigsson JF, Almqvist C, Bonamy A-KE, Ljung • Rickard, Michaëlsson K, Neovius M, et al. Registers of the Swedish total population and their use in medical research. Eur J Epidemiol [Internet]. [cited 2021 Oct 12];31. Available from: http://www.statistikdatabasen.scb.se

91. Ludvigsson JF, Svedberg P, Olén O, Bruze G, Neovius M. The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. Eur J Epidemiol 2019 344 [Internet]. 2019 Mar 30 [cited 2021 Oct 12];34(4):423–37. Available from: https://link.springer.com/article/10.1007/s10654-019-00511-8

92. Brooke HL, Talbäck M, Hörnblad J, Johansson LA, Ludvigsson JF, Druid H, et al. The Swedish cause of death register. Eur J Epidemiol [Internet]. 2017 Sep 1 [cited 2022 Mar 15];32(9):765. Available from: /pmc/articles/PMC5662659/

93. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. The Alcohol Use Disorders Identification Test Guidelines for Use in Primary Care. 2001;

94. Andersson T, Alfredsson L, Källberg H, Zdravkovic S, Ahlbom A. Calculating measures of biological interaction. Eur J Epidemiol. 2005;20(7):575–9.

95. Huang Z. Extensions to the k-means algorithm for clustering large data sets with categorical values. Data Min Knowl Discov [Internet]. 1998 [cited 2021 Jun 2];2(3):283–304. Available from: https://link-springer-com.proxy.kib.ki.se/content/pdf/10.1023/A%3A1009769707641.pdf

96. Huang Z. A Fast Clustering Algorithm to Cluster Very Large Categorical Data Sets in Data. J Biosoc Sci. 1992;24(4):463–75.

97. Ketchen DJJ, Shook CL. The Application Of Cluster Analysis In Strategic MAnagement Research: An analysis and critique. 1996;17:441–58.

98. Goodyear MD, Krleza-Jeric K, Lemmens T. The Declaration of Helsinki Mosaic tablet, dynamic document, or dinosaur? [Internet]. Vol. 335, British Medical Journal. 2007 [cited 2022 Mar 4]. p. 624–5. Available from: http://bmj.

99. WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects – WMA – The World Medical Association [Internet]. [cited 2022 Mar 5]. Available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

100. Fergusson DM, Horwood LJ. Does cannabis use encourage other forms of illicit drug use? Addiction. 2000;95(4):505–20.

101. Fergusson DM, Boden JM, Horwood LJ. Cannabis use and other illicit drug use: Testing the cannabis gateway hypothesis. Addiction. 2006;101(4):556–69.

102. Degenhardt L, Glantz M, Evans-Lacko S, Sadikova E, Sampson N, Thornicroft G, et al. Estimating treatment coverage for people with substance use disorders: an analysis of data from the World Mental Health Surveys. World Psychiatry [Internet]. 2017 Oct [cited 2019 Sep 23];16(3):299–307. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28941090

103. Buu A, Dabrowska A, Mygrants M, Puttler LI, Jester JM, Zucker RA. Gender differences in the developmental risk of onset of alcohol, nicotine, and marijuana use and the effects of nicotine and marijuana use on alcohol outcomes. J Stud Alcohol

Drugs [Internet]. 2014 [cited 2019 Mar 14];75(5):850–8. Available from: https://www.jsad.com/doi/pdf/10.15288/jsad.2014.75.850

104. Stenbacka M. Problematic alcohol and cannabis use in adolescence - Risk of serious adult substance abuse? Drug Alcohol Rev. 2003;22(3):277–86.

105. Woicik PA, Stewart SH, Pihl RO, Conrod PJ. The substance use risk profile scale: A scale measuring traits linked to reinforcement-specific substance use profiles. Addict Behav [Internet]. 2009 Dec 1 [cited 2019 Mar 26];34(12):1042–55. Available from: https://www.sciencedirect.com/science/article/pii/S0306460309001713

106. Otten R, Mun CJ, Shaw DS, Wilson MN, Dishion TJ. A developmental cascade model for early adolescent-onset substance use: the role of early childhood stress. Addiction. 2018;326–34.

107. Rioux C, Castellanos-Ryan N, Parent S, Vitaro F, Tremblay RE, Séguin JR. Age of Cannabis Use Onset and Adult Drug Abuse Symptoms: A Prospective Study of Common Risk Factors and Indirect Effects. Can J Psychiatry. 2018;63(7):457–64.

108. Halladay JE, Munn C, Boyle M, Jack SM, Georgiades K. Temporal Changes in the Cross-Sectional Associations between Cannabis Use, Suicidal Ideation, and Depression in a Nationally Representative Sample of Canadian Adults in 2012 Compared to 2002. Can J Psychiatry. 2019;

109. Hindley G, Beck K, Borgan F, Ginestet CE, McCutcheon R, Kleinloog D, et al. Psychiatric symptoms caused by cannabis constituents: a systematic review and meta-analysis. The Lancet Psychiatry [Internet]. 2020 [cited 2020 Mar 29];7(4):344–53. Available from: www.thelancet.com/psychiatry

110. Tullverket, Polismyndigheten. Drogsituationen: Lägesbild i Sverige 2013-2016. 2016.

111. Bartoli F, Crocamo C, Carrà G. Cannabis use disorder and suicide attempts in bipolar disorder: A meta-analysis [Internet]. Vol. 103, Neuroscience and Biobehavioral Reviews. Elsevier Ltd; 2019 [cited 2020 Sep 16]. p. 14–20. Available from: https://doi.org/10.1016/j.neubiorev.2019.05.017

112. Teesson M, Hall W, Lynskey M, Degenhardt L. Alcohol- and Drug-Use Disorders in Australia: Implications of the National Survey of Mental Health and Wellbeing. Aust New Zeal J Psychiatry [Internet]. 2000 Jun 26 [cited 2021 Oct 8];34(2):206–13. Available from: https://journals.sagepub.com/doi/full/10.1080/j.1440-1614.2000.00715.x

113. Manthey J, Freeman TP, Kilian C, López-Pelayo H, Rehm J. Public health monitoring of cannabis use in Europe: prevalence of use, cannabis potency, and treatment rates. Lancet Reg Heal - Eur [Internet]. 2021 Sep [cited 2021 Oct 8];0(0):100227. Available from: http://www.thelancet.com/article/S2666776221002131/fulltext

114. Freeman TP, Winstock AR. Examining the profile of high-potency cannabis and its association with severity of cannabis dependence. Psychol Med. 2015;45(15):3181–9.

115. Butterworth P, Slade T, Degenhardt L. Factors associated with the timing and onset of cannabis use and cannabis use disorder: Results from the 2007 Australian National Survey of Mental Health and Well-Being. Drug Alcohol Rev. 2014;33(5):555–64.

116. Kessler RC, Amminger GP, Aguilar-Gaxiola S, Alonso J, Lee S, Üstün TB. Age of onset of mental disorders: A review of recent literature. Curr Opin Psychiatry.

2007;20(4):359–64.

117. Kawa I, Carter JD, Joyce PR, Doughty CJ, Framtpon CM, Wells JE, et al. Gender differences in bipolar disorder: Age of onset, course, comorbidity, and symptom presentation. Bipolar Disord. 2005 Apr;7(2):119–25.

118. Solmi M, Radua J, Olivola M, Croce E, Soardo L, Salazar de Pablo G, et al. Age at onset of mental disorders worldwide: large-scale meta-analysis of 192 epidemiological studies [Internet]. Vol. 17, Molecular Psychiatry. 2021 [cited 2021 Oct 25]. p. 22. Available from: https://doi.org/10.1038/s41380-021-01161-7

119. SOU2021:93. Från delar till helhet. En reform för samordnade , behovsanpassade och personcentrerade insatser till personer med samsjuklighet, SOU 2021:93. 2021.

120. Gripe I, Danielsson AK, Ramstedt M. Are changes in drinking related to changes in cannabis use among Swedish adolescents? A time–series analysis for the period 1989–2016. Addiction [Internet]. 2018 Sep 1 [cited 2022 Mar 15];113(9):1643–50. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/add.14244

121. Sherman BJ, McRae-Clark AL, Baker NL, Sonne SC, Killeen TK, Cloud K, et al. Gender differences among treatment-seeking adults with cannabis use disorder: Clinical profiles of women and men enrolled in the achieving cannabis cessation—evaluating N-acetylcysteine treatment (ACCENT) study. Am J Addict [Internet]. 2017 Mar 1 [cited 2020 Mar 29];26(2):136–44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28152236

122. Dalman C, Bremberg S, Åhlen J, Ohlis A, Agardh E, Wicks S, et al. Psykiska besvär och psykiatriska tillstånd hos barn och unga – begrepp, mätmetoder och förekomst. En kunskapsöversikt [Internet]. 2021. Available from: https://forte.se/app/uploads/2021/12/kunskapso-versikt-begrepp-och-ma-tmetoder-barn-och-unga.pdf

123. Degenhardt L, Bharat C, Glantz MD, Sampson NA, Al-Hamzawi A, Alonso J, et al. Association of Cohort and Individual Substance Use with Risk of Transitioning to Drug Use, Drug Use Disorder, and Remission from Disorder: Findings from the World Mental Health Surveys. JAMA Psychiatry [Internet]. 2019 [cited 2019 Jun 18];76(7):708–20. Available from: https://jamanetwork-com.proxy.kib.ki.se/journals/jamapsychiatry/fullarticle/2727386

124. Forslund T, Kosidou K, Wicks S, Dalman C. Trends in psychiatric diagnoses, medications and psychological therapies in a large Swedish region: a population-based study. [cited 2021 Oct 12]; Available from: https://doi.org/10.1186/s12888-020-02749-z

125. Packness A, Waldorff FB, Christensen R de P, Hastrup LH, Simonsen E, Vestergaard M, et al. Impact of socioeconomic position and distance on mental health care utilization: a nationwide Danish follow-up study. Soc Psychiatry Psychiatr Epidemiol. 2017;52(11):1405–13.

126. Lundberg I, Damström Thakker K, Hällström T, Forsell Y. Determinants of non-participation, and the effects of non-participation on potential cause-effect relationships, in the PART study on mental disorders. Soc Psychiatry Psychiatr Epidemiol. 2005;40(6):475–83.

127. SPAK F, HALLSTROM T. Prevalence of female alcohol dependence and abuse in

Sweden. Addiction. 1995;90(8):1077–88.

128. Lövestad S. Intimate partner violence, sociodemographic factors and mental health among population based samples in Sweden.

129. Rothman KJ, Lash TL, Buehler JW, Cahill J, Gwinn M, Carolina N, et al. Modern epidemiology 3rd edition. 2008;13–5.

130. Manrique-garcia E, Zammit S, Dalman C, Hemmingsson T, Allebeck P. Cannabis use and depression: a longitudinal study of a national cohort of Swedish conscripts. BMC Psychiatry [Internet]. 2012;12(112). Available from: http://eds.a.ebscohost.com.e.bibl.liu.se/eds/pdfviewer/pdfviewer?sid=25493718-60a9-4442-9c5d-40c26fb42b68%40sessionmgr4004&vid=5&hid=4108

131. Andréasson S, Engström A, Allebeck P, Rydberg U. CANNABIS AND SCHIZOPHRENIA A Longitudinal Study of Swedish Conscripts. Lancet. 1987;330(8574):1483–6.

132. Hudson A, Hudson P. Risk Factors for Cannabis-Related Mental Health Harms in Older Adults: A Review [Internet]. Clinical Gerontologist. 2020 [cited 2020 Sep 17]. Available from: https://doi.org/10.1080/07317115.2020.1808134

133. Hindocha C, Norberg MM, Tomko RL. Solving the problem of cannabis quantification. The Lancet Psychiatry [Internet]. 2018 Apr 1 [cited 2022 Mar 27];5(4):e8. Available from: http://www.thelancet.com/article/S2215036618300889/fulltext

134. Amalie Rosendahl Jensen H, Karjalainen K, Juel K, Ekholm O. Consistency in Adults' Self-Reported Lifetime Use of Illicit Drugs: A Follow-Up Study Over 13 Ye ars [Internet]. 490 JOURNAL OF STUDIES ON ALCOHOL AND DRUGS. 2018 [cited 2019 Mar 14]. Available from: https://www.jsad.com/doi/pdf/10.15288/jsad.2018.79.490

135. The Swedish Council for Information on Alcohol and Other Drugs C. Drug Trends in Sweden 2017 CAN report 163. 2017.

136. Laursen B, Hoff E. Person-centered and variable-centered approaches to longitudinal data. Vol. 52, Merrill-Palmer Quarterly. 2006. p. 377–89.

137. Newcomer SR, Steiner JF, Bayliss EA. Identifying subgroups of complex patients with cluster analysis. Am J Manag Care [Internet]. 2011 [cited 2021 May 14];17(8). Available from: www.ajmc.com

138. Cornell JE, Pugh JA, Williams, Jr JW, Kazis L, Lee AFS, Parchman ML, et al. Multimorbidity Clusters: Clustering Binary Data From Multimorbidity Clusters: Clustering Binary Data From a Large Administrative Medical Database. Appl Multivar Res. 2009;12(3):163.

139. Moe FD, Moltu C, McKay JR, Nesvåg S, Bjornestad J. Is the relapse concept in studies of substance use disorders a "one size fits all" concept? A systematic review of relapse operationalisations. Drug Alcohol Rev [Internet]. 2021 Nov 18 [cited 2021 Nov 23]; Available from: https://pubmed.ncbi.nlm.nih.gov/34792839/

140. Håkansson A. En svensk modell att utmana. 2015;1–2.

141. Föreningen S psykiatriska. beroendemedicin i öppenvården. 2018.

142. Socialstyrelsen. Nationella riktlinjer för vård och stöd vid missbruk och beroende. 2015.

143. Luther AWM, Reaume S V, Qadeer RA, Thompson K, Ferro MA. Substance use disorders among youth with chronic physical illness. 2020 [cited 2022 Apr 7]; Available from: https://doi.org/10.1016/j.addbeh.2020.106517

144. Lees R, Hines LA, D'Souza DC, Stothart G, DI Forti M, Hoch E, et al. Psychosocial and pharmacological treatments for cannabis use disorder and mental health comorbidities: A narrative review [Internet]. Vol. 51, Psychological Medicine. Cambridge University Press; 2021 [cited 2021 Dec 18]. p. 353–64. Available from: https://www.cambridge.org/core/journals/psychological-medicine/article/psychosocial-and-pharmacological-treatments-for-cannabis-use-disorder-and-mental-health-comorbidities-a-narrative-review/42DC4AC75716B6AB115FE1EBA0D1F9C1

145. Blom B, Dukes KA, Lundgren L, Sullivan LM. Register data in the evaluation and program planning of addiction treatment programs: Using Sweden as an example. Eval Program Plann [Internet]. 2015 [cited 2022 Mar 12];49:185–91. Available from: http://dx.doi.org/10.1016/j.evalprogplan.2014.12.017

146. Manrique-Garcia E, Zammit S, Dalman C, Hemmingsson T, Andreasson S, Allebeck P. Prognosis of schizophrenia in persons with and without a history of cannabis use. Psychol Med. 2014;44(12):2513–21.

147. Andréasson S, Allebeck P. Cannabis and mortality among young men. Scand J Soc Med. 2009;18(1):9–15.

148. Di Forti M. To legalize or not to legalize cannabis, that is the question! Vol. 19, World Psychiatry. Blackwell Publishing Ltd; 2020. p. 188–9.

149. Rehm J, Manthey J. Cannabis and public health: a global experiment without control. World Psychiatry. 2020 Jun 1;19(2):192–4.

11 APPENDIX

Table A1. Overview of diagnostic criteria for CUD (including harmful use of cannabis, cannabis abuse and cannabis dependence) by diagnostic scheme.

	ICD-10	DSM-IV	DSM-5
	Harmful use of cannabis A pattern of cannabis use that is causing damage to health. The damage may be physical or mental. Cannabis dependence A cluster of behavioral, cognitive, and physiological phenomena that develop after repeated cannabis use and that typically include: 1) Strong desire to use cannabis. 2) Difficulties in controlling its use. 3) Withdrawal syndrome or using a (same/other) substance to prevent withdrawal. 4) Increased tolerance, as evidenced by diminished effect. 5) A higher priority given to cannabis use than to other activities and obligations. 6) Persisting in its use despite harmful consequences.	Cannabis abuse 1) Cannabis use interfering with social, occupational, or recreational activities. 2) Recurrent cannabis use in situations in which it is physically hazardous. 3) Recurrent cannabis use resulting in problems with law enforcement (e.g., being detained, arrested). 4) Continued cannabis use, despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of cannabis. Dependence 5) Tolerance, as evidenced by a markedly diminished effect. 6) Withdrawal syndrome or drinking to prevent withdrawal. 7) Cannabis is taken in larger amounts or over longer periods than intended. 8) Inability to cut down or reduce cannabis use. 9) Spending large amounts of time to obtain, use, or recover from the effects of cannabis. 10) Giving up important social, occupational, or recreational activities in favor of using cannabis. 11) Continued cannabis use despite knowledge of having a persistent or recurrent physical or psychological problem.	1) Important social, occupational, or recreational activities are given up or reduced because of cannabis use. 2) Recurrent cannabis use in situations in which it is physically hazardous. 3) Craving, or a strong desire or urge to use cannabis. 4) Continued cannabis use, despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of cannabis. 5) Tolerance, as evidenced by a markedly diminished effect. 6) Withdrawal syndrome or drinking to prevent withdrawal. 7) Cannabis is taken in larger amounts or over longer periods than intended. 8) Inability to cut down or reduce cannabis use. 9) Spending large amounts of time to obtain, use, or recover from the effects of cannabis. 10) Giving up important social, occupational, or recreational activities in favor of using cannabis. 11) Continued cannabis use despite knowledge of having a persistent or recurrent physical or psychological problem.
Notes	**Cannabis dependence:** 3 of the 6 criteria need to be met for the diagnosis of dependence. Criteria should be met within a 12-month period.	**Cannabis abuse:** 1 of symptoms 1-4. **Cannabis dependence:** 3 of symptoms 5-11. Criteria should be met within a 12-month period.	**CUD severity**: 2–3 symptoms indicates mild CUD; 4–5 symptoms indicates moderate CUD; and ≥6 symptoms indicates severe CUD. Criteria should be met within a 12-month period.