CONTRIBUTIONS TO THE EPIDEMIOLOGICAL RESEARCH ON POLYDRUG USE AND CANNABIS DEPENDENCE

By

Karl Christian Alcover

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ABSTRACT

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Prior studies on cannabis use disorder suggest that 'cannabis only' users might have different cannabis-related experiences compared to their polydrug counterparts. If so, these findings might have important public health implications to the extent that cannabis use prevalence increases as cannabis policies are liberalized. One result might be increased use of cannabis plus one or more other psychoactive drugs, in a pattern broadly termed "polydrug use" (McCabe et al. 2006). For perspective, recent estimates suggest that approximately 35% of adolescents in the United States (US) use more than one drug (Connell, Gilreath, and Hansen 2009). Recent cannabis policies that favor 'recreational' use might change this estimate.

In this dissertation research project on the topic of 'cannabis only' versus 'polydrug' users, there are three investigations, all of which focus on the occurrence of cannabis-related problems and experiences (PE). These problems and experiences encompass clinical features of cannabis use disorder (CUD) (e.g., cannabis dependence) and problems that might not be caused by any underlying pathological state. The first study aims to estimate the risk of cannabis-related PE, with contrasts between newly incident "cannabis only" users and newly incident cannabis users who use other internationally regulated drugs (IRD) soon after cannabis onset. The second study aims to identify cannabis-IRD latent classes among newly incident cannabis users without prior non-cannabis IRD use and to investigate the extent to which these subgroups might be more or less likely to develop cannabis dependence relatively soon after cannabis onset. The third study investigates covariations of CUD-related PE among newly incident cannabis users,

stratified by durations of cannabis use, in which duration is defined as the elapsed time from the month of cannabis onset to the quarter of survey assessment within a 12-month interval.

All of these studies share a common research approach, described in brief as follows. First, as is characteristic of all credible epidemiological studies that produce definitive evidence, there is a pre-specified study population. In this instance, the study population consists of non-institutionalized US civilian residents age 12 years and older, as sampled, recruited, and assessed each year for the National Surveys on Drug Use and Health (NSDUH). Second, after Institutional Review Board-approved consent procedures, all participants are assessed using confidential (but not anonymous) audio computer-assisted self-interviews. Within these self-interview sessions, there are cannabis and cannabis dependence modules, as well as modules on other drugs and health topics, with multi-item standardized questions. Estimates for all dissertation research projects are from public use data files based on these surveys, with analysis-weighted estimations and Taylor series linearization for variance estimation except where noted.

The main findings and implications, summarized across the three research projects, are as follows: (Study 1) Cannabis users who start using non-cannabis IRD soon after cannabis have greater risk of developing CUD-related problems and experiences; (Study 2) Three latent classes were identified (‘cannabis only’, ‘cannabis+analgesics’, and ‘cannabis+hallucinogens’), each of classes ‘cannabis+analgesics’ and ‘cannabis+hallucinogens’ was found to have greater risk of developing cannabis dependence compared to ‘cannabis only’ class; (Study 3) Clustering of CUD-related problems and experiences increases with durations of cannabis use. These findings merit further investigation. Limitations are described in detail in the dissertation Discussion section and conclusions are drawn, along with suggested directions for future research, which include longitudinal studies that build from this initial cross-sectional evidence.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

KEY TO ABBREVIATIONS

ACASI	Audio Computer-Assisted Self-Interviewing
Add Health	National Longitudinal Study of Adolescent to Adult Health
AIC	Akaike's Information Criterion
BIC	Bayesian Information Criterion
CAIC	Consistent Akaike's Information Criterion
CI	Confidence Interval
CUD	Cannabis Use Disorder
DSM	Diagnostic and Statistical Manual
IRD	Internationally Regulated Drugs
MTF	Monitoring the Future
NESARC	National Epidemiologic Survey on Alcohol and Related Conditions
NCS	National Comorbidity Survey
NSDUH	National Survey on Drug Use and Health
PCP	Phencyclidine
PE	Problem and Experience
SAHMSA	Substance Abuse and Mental Health Services Administration
US	United States
USP	United States Pharmacopeia
WHO	World Health Organization

CHAPTER 1: RATIONALE AND AIMS

1.1 Rationale

There is a growing body of literature suggesting that users of single drug might have different drug-related experiences, as compared to their polydrug-using counterparts (Lopez-Quintero and Anthony 2015b; Leeman et al. 2016; Bhalla, Stefanovics, and Rosenheck 2017). In most cases, the use of multiple drugs is linked to more adverse drug-related outcomes. Implicit in the comparisons between two subgroups defined by various combinations of drugs is the notion that the use of one drug might influence effects of another drug, resulting in a different experience that otherwise would not occur when using either of the drugs alone.

In the United States (US), policy changes that influence occurrence of recreational use of drugs such as cannabis have prompted increased attention to the idea that there might be shifts in the occurrence of cannabis-related adversities. These shifts are central in this dissertation research project, which explores variations observed across subgroups characterized by the use of multiple internationally regulated drugs (IRD), with a focus on cannabis use and cannabis-related outcomes (e.g., cannabis dependence).

This dissertation work falls squarely within the domain of epidemiological research cannabis dependence and its complexities as might be complicated when polydrug use occurs. The three research projects completed for this dissertation research address gaps in scientific knowledge about the topics pertinent to polydrug use and cannabis dependence.

1.2 Specific Aims

It is possible to state the specific aims of this dissertation research project in relation to three studies completed to date, with each project as described below.

1.2.1 Manuscript 1

Primary aim: To estimate the risk of cannabis-related problems and experiences (PE) as the risk might differ across subgroups of newly incident "cannabis only" users versus newly incident cannabis users who use other internationally regulated drugs (IRD) soon after cannabis onset. ***Secondary aim:*** To investigate variations in estimated risk of cannabis-related problems and experiences (PE) among drug-specific cannabis-IRD subgroups (e.g., newly incident cannabis users who started using cocaine soon after cannabis onset).

1.2.2 Manuscript 2

Primary aim: To identify latent classes observed among newly incident cannabis users with and without prior non-cannabis IRD use and to investigate the extent to which membership in these subgroups might be associated with developing cannabis dependence within an interval of approximately 12 months. ***Secondary aim:*** In a methodological inquiry, to investigate potential heterogeneity in latent class probabilities between two sets of NSDUH data of nationally representative samples from the same study population.

1.2.3 Manuscript 3

Primary aim: To investigate covariation of CUD-related problems and experiences among newly incident cannabis users over durations of cannabis use, in which duration is defined as the elapsed time from the month of cannabis onset to the quarter of survey assessment within a 12-month interval.

CHAPTER 2: BACKGROUND AND REVIEW OF THE LITERATURE

The purpose of this chapter is to set the stage for the projects and specific aims just mentioned. This chapter provides background information pertinent to cannabis epidemiology. It includes information about the history of cannabis as an agricultural product of interest to humans for several different reasons. It also covers facets of evidence about the epidemiology of cannabis use and the epidemiology of cannabis use disorders, with focus on the construct of cannabis dependence and the problems and experiences that are encountered as 'sub-threshold' manifestations of the progress from first cannabis use until occurrence of a cannabis dependence syndrome.

2.1 Background

2.1.1 Cannabis Plant

The cannabis plant, also known as hemp, (marijuana; *Cannabis sativa* L.) is a highly adaptive annual plant that grows in temperate and tropical regions. Typically, cannabis plant reaches maturity within 3-5 months in its normal environment and around 60 days when grown indoors. The plant is characterized by its finely-branched leaves divided into multiple sharp-edged leaflets and woody, hairy stem that can grow 15 feet or higher, depending on variety and growing conditions (Iversen 2007).

The botanist Carl Linnaeus focused attention upon *cannabis sativa* in his 18th century studies, but there are other species, as described by Watts (2006). In addition, before Linnaeus' botanical work, there is historical evidence of cannabis being used for (1) entheogenic or intoxicating purposes, (2) medicinal purposes, and (3) production of rope and clothing from cannabis (hemp) fibers. The entheogenic uses of cannabis date back some 4500-5000 years, according to speculations offered by Russo and colleagues based on their inspection of ancient Chinese

artifacts (Russo et al. 2008), and Li (1973) documented other ancient uses of cannabis by inhabitants of the mountain ranges of central Asia as long as 7000 years ago.

In ancient times hemp was cultivated for the manufacture of various products such as ropes, nets, and clothes (Iversen 2007). More recently, cannabis plants have been cultivated for several economic purposes including hemp production, oil production, and other industrial uses – some are grown for production of their psychoactive contents. Psychoactive potency varies widely based on genetics and environmental conditions where the plant is grown.

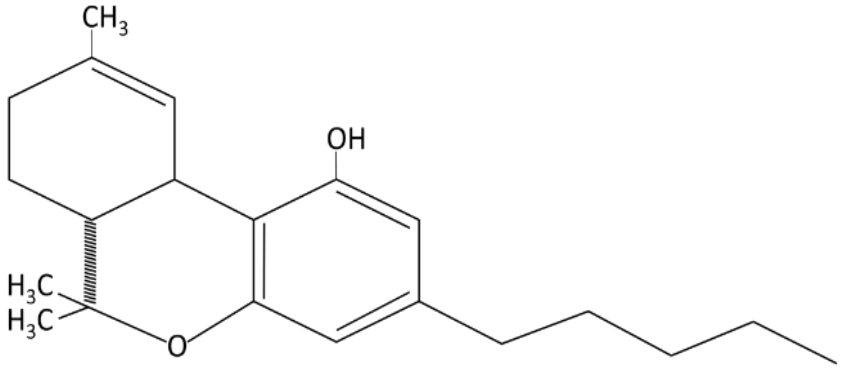
Psychoactive properties of cannabis vary across and within species. Some of the cannabis species that are useful for rope and clothing appear to have little or no psychoactive effects when consumed by humans. Recent cannabis genetics and crop breeding has been an activity that has increased the potential for entheogenic and intoxicating purposes, which encompass the use of this plant or its compounds 'to get high' or to enter into spiritual experiences judged by the users to bring them closer to enlightenment or connections with deities.

2.1.2 Pharmacology of Cannabinoids

Among the many chemical compounds found in cannabis, cannabinoids comprise class of compounds unique to cannabis plants. *C. sativa* has more than 80 known cannabinoid compounds (ElSohly and Slade 2005). In the human body, cannabinoids bind with cannabinoid receptors in the endocannabinoid system. The receptor binding is followed by modulation of various processes related to relaxation, diet, sleep, memory, and immunity (Di Marzo 1998).

Although the pharmacological effects of cannabinoids derived from cannabis have been known for thousands of years, it has been only during the first half of the 19th century that chemists have extracted specific drug compounds that elucidate specific cannabinoid effects and properties (Iversen 2007). Elucidation of the major cannabis psychoactive agent, (-)Δ^9-6a,10a-

Figure 2.1. Delta-9-Tetrahydrocannabinol.



trans-tetrahydrocannabinol (Δ^9-THC), commonly known as THC (Figure 1), occurred roughly 60-70 years ago (Gaoni and Mechoulam 1964; Radwan et al. 2009).

THC is present in most parts of cannabis plant but is highly concentrated in resin produced by glandular trichrome at the base of the leaves, stem and buds (Kim and Mahlberg 1997). THC concentration is greatest in oil from flower buds, intermediate in bracts, leaves, stems and roots. It is lowest in seeds (Fetterman et al. 1971). It is claimed that THC potency in street-supplied cannabis has increased up to 30 fold (Mehmedic et al. 2010), and the increase is attributed to crop genetics and breeding toward phenotypes that have commercial value.

2.1.3 Medical Use and Extra-Medical Cannabis Use

The US has a long history of cannabis regulation, which originated during the early 18th-19th century years as the US emerged from its colony status in relation to Great Britain, at which time farmers were encouraged to plant cannabis for hemp production used in manufacture of rope and clothing (Bonnie and Whitebread 1974). Anti-cannabis federal legislation was enacted in the early 20th century when a federal tax authority was used to prohibit cultivation, possession, and use of cannabis products, based on a rationale that mixed fairly flimsy toxicological evidence with an intent to exert social control over racial-ethnic minority groups, among whom cannabis smoking was a noteworthy recreational activity (*ibid*.).

In 1970, the federal Controlled Substances Act (CSA1970) declared that cannabis had no approved medical use, despite centuries of its appearance in the pharmacopeia, and without rigorous evaluation by standards of the US Food and Drug Administration. Cannabis and cannabinoids were assigned to Schedule I of CSA1970, along with heroin, LSD, and other banned compounds (Bonnie and Whitebread 1974).

Since that time, even though a US Presidential Commission urged decriminalization of cannabis possession and use, there have been unsuccessful efforts to move cannabis from Schedule I of the federal legislation to Schedule II or lower schedules (drugs with a high potential for abuse, with use potentially leading to severe psychological or physical dependence). The only exceptions have involved compounds derived from cannabis, for which lower levels of regulation have been allowed in strictly limited contexts (e.g., Marinol, dronabinol, which is assigned to Schedule III).

During the interval from 1970 to the present time, some local sub-state jurisdictions have decided to 'fly below the federal radar' in a deliberate effort to discourage their law enforcement officials from spending time on arrest and prosecutions of cannabis-possessing or cannabis-using citizens of their communities. Noteworthy 'scoff-law' ordinances (with respect to federal legislation) have prevailed in various places, perhaps most notably the university communities within which the University of Wisconsin and University of Michigan are located. These local attitudes and norms were forerunners of what became a 'medical marijuana law' advocacy during the years from the mid-1990s through to the present decade.

The legality of cannabis use for medical purposes was first established in California under the Compassionate Use Act in 1996, often characterized as a 'Medical Marijuana Law'

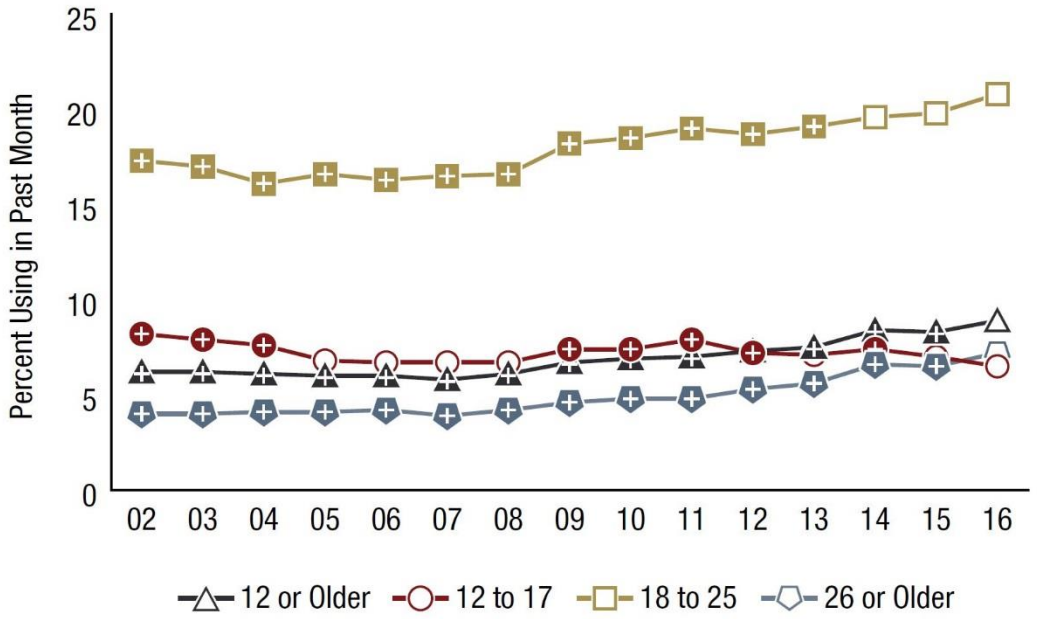
(MML). Subsequently, 29 States and Washington D.C. have legalized the use of cannabis for medical purposes and have their own MML laws.

Relative to the roughly 25 million US residents who currently use cannabis, about three million use cannabis based on MML-authorizations. Roughly 80% of the MML-authorized users reside in states where medical marijuana is legal (Compton et al. 2017). Among adult cannabis users, the current proportion of medical cannabis users ranges from 10%-18% (Lin et al. 2016; Compton et al. 2017)

The possibility that legalizing medical cannabis use might prompt increased frequency of cannabis use has been a controversial topic. In some recently published research, MML-authorized cannabis users have been observed to have greater odds of illegal cannabis use and are more likely to have developed a cannabis dependence syndrome (Cerdá et al. 2012). Other studies suggest no such difference (Khatapoush and Hallfors 2004; Hasin, Wall, et al. 2015; Sarvet et al. 2018).

For clarification, it might be useful to draw a distinction between 'medical use' of a drug versus 'extra-medical use.' The 'extra-medical use' concept refers to taking the drug for a feeling state such as to get high or using more frequently or in a larger dose than prescribed – i.e., outside the boundaries of medically prescribed uses. In some instances, 'extra-medical use' might be considered by the user to be use for a 'medical' reason (e.g., relief of a subjectively felt problem) that falls beyond the boundaries of a prescriber's intent, but in many instances, extra-medical (EM) uses include using the drug 'to get high' and for related feeling states (Parker 2016).

Figure 2.2. Pattern of Past Month Cannabis Use Among People Aged 12 or Older, by Age Group. Data from National Survey on Drug Use and Health, 2002-2016.



+ Difference between this estimate and the 2016 estimate is statistically significant at the .05 level.

In most surveys on national representative US samples, EM cannabis use is not differentiated from medical cannabis use. For example, assessments made for the US National Surveys on Drug Use and Health have not generally asked about medical cannabis use, and it was not until 2013 that specific MML-authorized use was assessed via NSDUH standardized questions. A study conducted by (Lin et al. 2016) based on NSDUH 2013 data suggests that almost 20% of cannabis users in the US are using cannabis medically. Irrespective of the purpose of use, an increasing prevalence of cannabis use has been observed. Figure 2.2 shows the pattern of past-month cannabis use among cannabis users across various age groups. Most are extra-medical cannabis users during these years (United States 2017b).

2.2 Cannabis Use Disorder and Cannabis Dependence

Cannabis use disorder (CUD) is defined as 'problematic cannabis use leading to clinically significant impairment or distress manifested by impaired control, continued use despite social/medical problems, craving, tolerance and withdrawal" and encompasses cannabis "abuse" and dependence. (American Psychiatric Association, 2013). Generally, diagnosis of cannabis dependence requires meeting three or more of Diagnostic and Statistical Manual (DSM) criteria, composed of cannabis-related clinical features. Cannabis users who have problems but do not qualify as cannabis dependence cases might qualify as cases of 'cannabis abuse,' but this distinction is not crucial to this dissertation research project. This dissertation focuses on the occurrence of cannabis problems and experiences that might or might not occur in the context of a cannabis dependence syndrome. That is, many of the cannabis users will report problems and experiences that are not caused by any underlying pathological state such as cannabis dependence. For this reason, these problems and experiences cannot be said to be 'symptoms' of a cannabis use disorder. For this reason, they are characterized and labeled as 'problems and experiences' (e.g., in order to avoid over-medicalization of problems and experiences that are not manifestations of underlying pathological processes).

Until recently, diagnosis of cannabis use disorder excluded withdrawal as a cannabis dependence symptom (Table 2.1) (American Psychiatric Association 2013). Prior to the 1980s, cannabis was not generally considered a drug that causes drug dependence. In contrast with alcohol users and opioid users, cannabis users did not seem to experience withdrawal symptoms, which was a clinical feature that is common across other drug dependence diagnoses (Hall and Pacula 2003). Much of the evidence of cannabis-induced withdrawal symptoms has its basis in pre-clinical research. Most of the prior human studies are limited by self-reported symptoms and

are confounded by polydrug use among the cannabis users being studied (Wiesback et al. 1996; Bonnet and Preuss 2017).

A general re-conceptualization of cannabis dependence occurred between 1970 and 1990, after publication of an influential paper on the alcohol dependence syndrome (Edwards and Gross 1976; Edwards, Arif, and Hadgson 1981). This paper focused on alcohol, but offered a syndrome definition that had resonance with clinicians treating patients affected by other drug problems, including cannabis problems. In consequences, a revised definition for cannabis dependence reduced the importance of withdrawal symptoms, as reflected on DSM editions after 1980. Table 2.1 presents the DSM- and ICD-based diagnostic criteria for substance use disorder and cannabis dependence.

2.3 Epidemiology of Cannabis Dependence

Most of what we know about the epidemiology of cannabis dependence comes from studies conducted in the United States, with some noteworthy exceptions from studies in Germany and in New Zealand. For this section of the dissertation background chapter, attention is focused upon evidence based on recent studies on epidemiology of cannabis dependence in the US. These studies provide an evidence base upon which it is possible to build new research. Whether the experiences of cannabis users in Germany or New Zealand apply in research on cannabis users in the US is uncertain.

As with research on other diseases and outcomes, cannabis dependence research can be organized and presented based on the rubrics of epidemiology (Van Etten and Anthony 1998). Each rubric concerns significant aspect of epidemiological research that encompasses one of the five broad questions that characterize cannabis dependence. Table 2.2 shows a summary of the five rubrics of epidemiology, as applied in cannabis dependence.

Table 2.1. Diagnostic criteria for drug dependence, cannabis dependence and substance use disorder based on the Diagnostic and Statistical Manual (DSM-III, -IV, and -5) and based on the World Health Organization (WHO) International Classification of Diseases (ICD-10).

	DSM-III Drug Dependence	**ICD-10 Cannabis Dependence**	**DSM-IV Cannabis Dependence**	**DSM-5 Substance Use Disorder**
Tolerance	X	X	X	X
Taken larger amount or longer period than intended	X	**X**	X	X
Persistent but failed efforts to cut down or control use	X		X	X
More time spent to get or use	X	X	X	X
Given up or reduced activities	X	X	X	X
Continued use despite physical or psychological problems	X	X	X	X
Withdrawal	-[b]	**X**	-	X
Used to relieve or avoid withdrawal symptoms.	X		-	-
Craving	-	X	-	X
Legal problems	-	-	-	-
Failed to fulfil major roles	X	-	-	X
Persistent use despite social or interpersonal problems	-	-	-	X
Persistent use in hazardous situation	-	-	-	X
Number of criteria to meet for diagnosis	≥3	≥3	≥3	≥2
Required duration of co-occurrence within past year	≥ 1 month	anytime	≥ 1 month	anytime

[b] Not applied to cannabis, hallucinogens or PCP.

Table 2.2. The five rubrics of epidemiology, as applied to cannabis dependence.

The Rubrics	Description	Questions
Quantity	Quantification of the disease burden	How many are cannabis dependent?
Location	Variations in occurrence in relation to certain characteristics (e.g., geographical location, age, sex)	Where are the cannabis dependents more likely to be found?
Causes	Explanation on what accounts for becoming a case	What accounts for some people in the community becoming cannabis dependent while other do not?
Mechanisms	Linkage between possible causal determinant and the condition of interest	What linkages of states and processes influence who becomes and remains a cannabis dependent?
Prevention and Control	Intervention that might reduce the occurrence of the condition	What can be done to prevent and intervene?

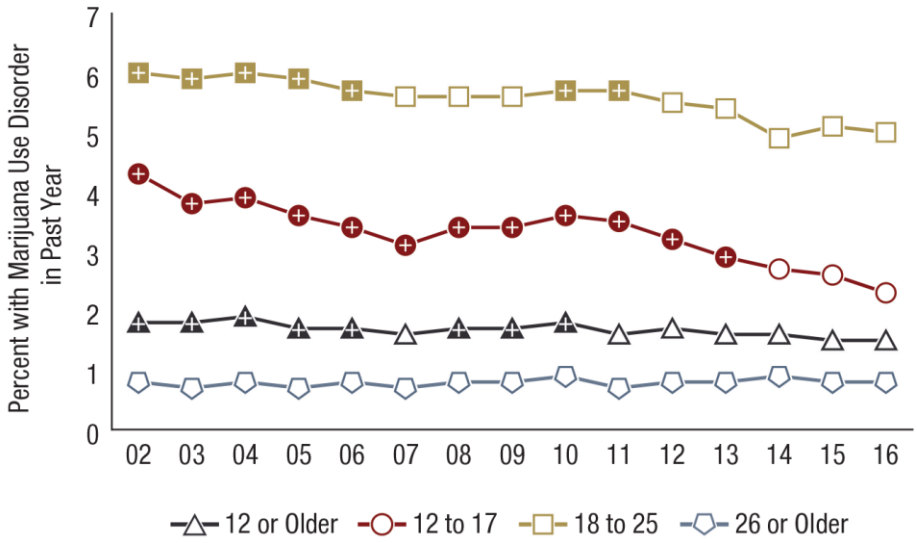
2.3.1 Quantity – How Many Are Affected?

A number of surveys on nationally representative samples collects information that allows the estimation of the prevalence and incidence of cannabis use disorder ("abuse" and dependence) in the US with carefully designed protocols that are constantly improved to promote accuracy. For this section, estimates are obtained mostly from surveys on nationally representative samples including National Survey on Drug Use and Health (NSDUH), National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), National Comorbidity Survey (NCS), National Longitudinal Study of Adolescent Health (Add Health), and Monitoring the Future (MTF). However, even with national surveys, research on cannabis dependence face challenges related to heterogeneity in study design, study population, and differences in cannabis dependence definition across DSM editions (Wittchen et al. 2008; Schlossarek et al. 2016; J. Anthony, Lopez-Quintero, and Alshaarawy 2017).

The prevalence estimates of cannabis use disorder in the US based on NSDUH data have been published recently by Substance Abuse and Mental Health Service Administration (United States 2017b). Figure 2 shows the cumulative incidence estimates of various age groups from 2002 to 2016. Among individuals age 12 or older, there is a statistically significant decline in the estimates from 1.8% in 2002 to 1.5% 2016. The decreasing estimates were also seen among individuals age 12-17 (4.3% in 2002 to 2.3% in 2016) and among individuals age 18-25 (6.0% in 2002 to 5.0% in 2016) but not among age 26 and older (0.8% in 2002 and 0.8% in 2016). According to NESARC, the prevalence estimate of cannabis use disorder among individuals age 18 and older increased from ~1.5% in 2001-2002 to ~3.0% in 2012-2013 (Hasin et al. 2016; Degenhardt, Cheng, and Anthony 2007). Among age 24-32, the prevalence estimate is ~4% based on Add Health Wave IV data (Haberstick et al. 2014).

Turning to cannabis dependence, approximately 0.3% of the US population experience DSM-IV cannabis dependence (Degenhardt, Cheng, and Anthony 2007; Delker, Brown, and Hasin 2015). Almost 9% of cannabis users age 18 and older develop DSM-IV cannabis dependence at some point in their life, and more than a third of them developed dependence within the first year of cannabis use(Lopez-Quintero et al. 2011; Wu, Zhu, and Swartz 2016). Slightly lower estimates of ~6%-8% were observed for cannabis users of the same age group who have used cannabis within 10 years after the initial use (Lopez-Quintero et al. 2011). Among age 24-32, the prevalence estimate is 8.3% based on Add Health Wave IV data (Haberstick et al. 2014). Similar estimate of ~ 9% for DSM-III cannabis dependence was observed among cannabis users age 15-54 who have used cannabis at least once based on the National Comorbidity Survey (J. C. Anthony, Warner, and Kessler 1994). The risk estimate of developing cannabis use disorder among cannabis users whose onset of cannabis use occurred

Figure 2.3. Cannabis Use Disorder in the Past Year among People Aged 12 or Older, by Age Group: Percentages, 2002-2016. Data from National Survey on Drug Use and Health, 2002-2016.



+ Difference between this estimate and the 2016 estimate is statistically significant at the .05 level.

within an interval of 12 months is 16.8% (Forman-Hoffman, Glasheen, and Batts 2017a). The probability transition from cannabis onset and cannabis dependence within 12 months after cannabis onset among individuals age 18 and older is 2% (Lopez-Quintero et al. 2011).

The risk estimate of cannabis dependence based on lifetime history data ranges from 1%-3% 12 months after cannabis onset among cannabis users age 15-54, while 2%-5% when the interval is 24 months (Wagner and Anthony 2002a). The estimate is 4% for individuals age 12 and older within 24-months after initiation (C.-Y. Chen, O'Brien, and Anthony 2005).

2.3.2 Location – Where Do We Find Variation in the Occurrence of Cases?

In several characteristics, there is an excess occurrence of cannabis dependence. Such characteristics include geography, sex or gender, race or ethnic self-identification, and social economic status.

Variation by geographic location

Substantial variation in the prevalence of cannabis use disorder by US states has been observed. Table 2.3 shows the prevalence estimates of cannabis use disorder in each state in the US from 2009-2014. Based on the estimates in 2009-2010, South Dakota and Virginia have the highest occurrence of cannabis use disorder (20.1%). Based on the most recent year-pair (2013-2014), Mississippi has the highest occurrence of cannabis use disorder (18.6%), followed by West Virginia (16.7%) and Delaware (16.6%). Generally, by looking at the point estimates, the prevalence of cannabis use disorder declined from 2009-2010 to 2013-2014. However, recent findings suggest that cannabis use disorder is approximately twice more prevalent in states with legal medical marijuana use (1.8; 95%CI=1.2, 2.7) (Cerdá et al. 2012).

Variation by sociodemographic characteristics

Age has been found to be associated with the risk of developing cannabis dependence (K. Chen and Kandel 1995; Gfroerer, Wu, and Penne 2002). A recent study by (Richter, Pugh, and Ball 2017) provides recent findings on the variations of cannabis dependence by age. Although interpretability of the estimates might be questionable due to model adjustment of non-confounding covariates of age, they reported that, among past-year cannabis users, individuals age 12-17 have almost twice the odds of developing cannabis dependence compared to cannabis users age 18-25 and almost four times the odds as compared to cannabis users age 26-44. An earlier study reported that 75% of cannabis onsets occur between ages 13 and 18, and that 20% of those who initiated marijuana before the age 15 are identified as having cannabis use disorder, while 10% for those who started after the age 15 (Gfroerer, Wu, and Penne 2002). These findings are consistent to earlier findings suggesting that the younger age of cannabis onset is

associated with greater likelihood of developing cannabis dependence (e.g., J. C. Anthony and Petronis 1995; Wayne Hall and Degenhardt 2009).

With respect to biological sex, excess occurrence of cannabis dependence among males compared to females has been documented (e.g., Stinson et al. 2006; C.-Y. Chen, O'Brien, and Anthony 2005; Wagner and Anthony 2007; Cotto et al. 2010). Using the National Household Survey on Drug Abuse data, Chen, O'Brien, and Anthony (2005) found male excess occurrence of cannabis dependence among lifetime cannabis users who are recently active users. However, they did not find male-female risk difference in cannabis dependence within 24-month after cannabis initiation. A later study conducted by Wagner and Anthony (2007) using NCS data found male-female differences in the risk of developing cannabis dependence during the first few years after cannabis onset, with excess risk occurring among male cannabis users. These findings are also supported by the findings of recent studies. For example, a study conducted by Lopez-Quintero et al. (2011) using NESARC data suggested that males age 18 years and older are more likely to develop cannabis dependence compared to females (HR = 1.4; 95% CI = 1.1,1.9). Haberstick et al. (2014) reported based on lifetime history data of individuals age 24-32 that males have greater odds of developing cannabis dependence than females (OR=1.4; 95% CI = 1.1, 1.8). These observed differences require further investigation as to what mechanisms might explain them. Understanding potential underlying mechanisms might also help explain male-female differences in various cannabis-related outcomes such as loss of appetite, improved memory and enthusiasm (e.g., Cuttler, Mischley, and Sexton 2016).

Variations in the occurrence of cannabis dependence has also been observed among self-identified racial or ethnic groups (e.g., Wu et al. 2011; Hasin et al. 2017). Excess occurrence of cannabis dependence was observed among Black Americans, Native-Americans and mixed-race

individuals compared to White Americans, while less occurrence was observed among Asian Americans and Native Hawaiian/Pacific Islanders (Wu, Zhu, and Swartz 2016). With respect to education and social economic status, individuals with college degree or higher are less likely to develop cannabis dependence (Wu, Zhu, and Swartz 2016), and individuals with family income less than $20,000 are more likely to develop cannabis dependence (Chen, O'Brien, and Anthony 2005).

Various other factors are associated with increased risk of cannabis dependence. These factors include use of other drugs, dependence on other drugs, negative life events, depression, exposure to parental disorder, conduct disorder, bipolar disorder, and other psychiatric disorders (Compton WM et al. 2007; van der Pol et al. 2013a; Hines et al. 2016; Lopez-Quintero et al. 2011; Yule et al. 2018).

2.3.3 Causes and Mechanisms

This section provides biological and social suspected reasons and linkages to why some individuals progress to cannabis dependence after first time cannabis use. Several of the characteristics mentioned above as facets of 'location' can be considered as suspected causal influences when the sequential timing of events is established, that is; they occur prior to the onset of cannabis dependence. Cannabis, however, is a necessary cause of cannabis dependence (Anthony, Lopez-Quintero, and Alshaarawy 2017). The development of cannabis dependence requires initiation of cannabis use, which might be followed by a series of behavioral events that sometimes involves experimental use that progresses to chronic use and onset of cannabis dependence (Bierut 2011), as with other types of drug dependence. There are other numerous suspected causal influences that might explain why some cannabis users progress from initiation to onset of cannabis dependence. Some of which include death of the family, use of other drugs,

Table 2.3. State-level prevalence estimate of cannabis use disorder. Data are from the National Surveys on Drug Use and Health, 2002-2014.

State	2009-2010 % (95% CI)	2010-2011 % (95% CI)	2011-2012 % (95% CI)	2012-2013 % (95% CI)	2013-2014 % (95% CI)	State	2009-2010 % (95% CI)	2010-2011 % (95% CI)	2011-2012 % (95% CI)	2012-2013 % (95% CI)	2013-2014 % (95% CI)
Alabama	15.5 (9.9-23.6)	13.2 (8.6-19.7)	13.2 (8.2-20.6)	16.3 (9.4-26.8)	12.4 (7.1-20.7)	**Montana**	12.3 (9.3-16.1)	10.9 (7.7-15.2)	12 (8.7-16.4)	11.2 (7.2-17.2)	9.8 (6.2-15.1)
Alaska	7.8 (5.8-10.6)	8.5 (6.1-11.6)	8.6 (6.1-12.1)	9.0 (6.3-12.5)	11.9 (7.6-18.0)	**Nebraska**	9.8 (5.7-16.2)	* (*-*)	18.4 (11.1-29.0)	16.2 (10.9-23.2)	14.2 (9.8-20.2)
Arizona	16.5 (11.4-23.2)	18.5 (13.8-24.3)	17.7 (13.7-22.6)	15.8 (11.2-21.9)	16.0 (11.4-22.1)	**Nevada**	15.2 (9.6-23.2)	16.2 (10.0-25.4)	12.6 (7.7-20.0)	8.4 (5.6-12.3)	9.5 (6.8-13.0)
Arkansas	14.0 (9.0-21.2)	13.3 (9.3-18.8)	21.9 (14.2-32.3)	21.8 (14.0-32.4)	11.9 (8.6-16.2)	**New Hampshire**	13.3 (9.3-18.7)	13.1 (9.4-17.9)	11.3 (8.0-15.7)	10.0 (7.0-14.1)	8.2 (5.8-11.5)
California	16.3 (13.9-19.0)	14.7 (12.5-17.3)	15.0 (12.8-17.5)	14.0 (11.9-16.5)	12.9 (11.2-14.8)	**New Jersey**	12.6 (8.0-19.3)	13.9 (9.9-19.3)	13.5 (9.1-19.6)	10.1 (6.5-15.4)	10.6 (7.1-15.5)
Colorado	11.2 (8.3-15.0)	11.6 (8.5-15.5)	13.7 (10.0-18.6)	11.0 (7.9-15.2)	10.0 (7.3-13.5)	**New Mexico**	16.4 (11.5-23.0)	15.4 (11.3-20.7)	13.8 (10.0-18.9)	18.4 (12.8-25.6)	16.5 (11.1-23.8)
Connecticut	12.4 (8.4-18.0)	11.6 (6.6-19.7)	14.3 (9.1-21.6)	12.6 (8.4-18.4)	10.9 (7.1-16.3)	**New York**	14.9 (12.5-17.8)	14.3 (11.7-17.5)	13.1 (10.9-15.7)	12.2 (10.2-14.5)	11.6 (9.5-14.1)
Delaware	14.9 (10.3-21.0)	11.5 (7.9-16.4)	12.3 (8.5-17.4)	15.9 (10.1-24.1)	16.6 (10.8-24.7)	**North Carolina**	18.6 (12.9-26.0)	16.5 (11.1-23.7)	16.3 (11.6-22.5)	18.4 (13.5-24.4)	13.9 (9.7-19.3)
D.C.	18.2 (11.2-28.1)	14.2 (9.7-20.4)	12.1 (8.5-16.8)	11.3 (8.0-15.8)	11.4 (7.9-16.0)	**North Dakota**	10.6 (7.1-15.6)	12.9 (9.1-18.1)	19.4 (13.5-27.1)	20.7 (13.3-30.6)	15.8 (10.2-23.6)
Florida	16.3 (13.5-19.5)	14.4 (11.9-17.2)	13.4 (10.9-16.3)	12.9 (10.2-16.0)	11.1 (9.2-13.4)	**Ohio**	16.9 (14.2-19.9)	15.8 (13.1-18.8)	13.9 (11.6-16.5)	12.7 (10.4-15.5)	11.7 (9.1-15.0)
Georgia	9.5 (6.3-14.1)	13.3 (8.8-19.8)	12.3 (8.3-18.0)	* (*-*)	* (*-*)	**Oklahoma**	17.2 (12.0-24.0)	14.5 (9.5-21.7)	12.4 (8.2-18.2)	10.2 (6.6-15.4)	9.3 (6.1-13.8)
Hawaii	17.5 (11.0-26.8)	12.5 (7.5-20.0)	10.7 (7.5-15.0)	11.7 (8.0-16.7)	10.7 (7.3-15.4)	**Oregon**	12.7 (9.3-17.2)	13.9 (10.7-17.9)	11.6 (8.6-15.6)	11.5 (8.0-16.3)	11.3 (8.1-15.6)
Idaho	16.2 (11.3-22.7)	12.3 (8.1-18.1)	8.9 (6.1-13.0)	12.0 (7.4-18.9)	14.7 (9.5-22.0)	**Pennsylvania**	15.1 (12.3-18.4)	16.9 (13.6-20.8)	14.6 (11.7-18.1)	13.0 (10.6-15.8)	12.2 (9.9-14.9)
Illinois	14.7 (12.7-17.1)	13.8 (11.5-16.4)	12.6 (10.3-15.3)	10.4 (8.6-12.6)	11.3 (9.1-14.0)	**Rhode Island**	14.4 (10.7-19.2)	11.1 (7.3-16.3)	9.5 (6.5-13.7)	11.6 (8.3-16.1)	12.6 (8.9-17.5)
Indiana	17.9 (13.3-23.6)	12.6 (9.1-17.3)	11.8 (7.7-17.7)	16.6 (11.4-23.6)	12.5 (9.1-17.0)	**South Carolina**	13.2 (8.4-20.1)	14.2 (9.8-20.3)	15.1 (10.3-21.7)	16.0 (10.6-23.5)	12.6 (8.9-17.6)
Iowa	13.1 (8.8-19.1)	15.9 (10.0-24.4)	15.2 (9.6-23.1)	11.6 (6.1-20.9)	11.4 (7.2-17.4)	**South Dakota**	20.1 (12.9-29.9)	16.3 (9.6-26.2)	14.7 (9.4-22.1)	12.3 (8.1-18.3)	16.1 (11.6-22.0)
Kansas	15.3 (9.7-23.3)	17.5 (11.3-26.2)	16.7 (10.3-25.9)	13.4 (8.3-21.1)	11.0 (7.1-16.6)	**Tennessee**	18.3 (12.6-25.7)	18.8 (12.6-26.9)	14.1 (8.9-21.7)	10.3 (6.0-17.2)	8.6 (5.6-12.9)
Kentucky	13.2 (8.7-19.5)	12.2 (8.1-17.9)	14.4 (10.2-19.9)	14.4 (9.1-21.8)	11.9 (7.6-18.2)	**Texas**	16.2 (13.2-19.7)	17.4 (14.3-21.0)	16.6 (13.6-20.1)	14.4 (11.9-17.3)	13.8 (11.3-16.8)

Table 2.3 (cont'd)

State	2009-2010	2010-2011	2011-2012	2012-2013	2013-2014	State	2009-2010	2010-2011	2011-2012	2012-2013	2013-2014
Louisiana	16.0 (10.8-23.1)	16.5 (10.6-24.6)	13.2 (8.7-19.5)	12.3 (8.6-17.2)	11.9 (8.1-17.2)	**Utah**	15.8 (9.4-25.4)	22.1 (14.2-32.8)	18.5 (12.4-26.6)	15.4 (10.6-21.8)	16.5 (11.9-22.4)
Maine	9.9 (6.7-14.6)	5.6 (3.8-8.2)	8.3 (5.5-12.2)	7.7 (5.4-10.8)	6.4 (4.8-8.6)	**Vermont**	14.5 (8.5-23.8)	14.3 (9.7-20.7)	13.2 (9.1-18.9)	10.1 (7.1-14.2)	13.2 (9.5-18.0)
Maryland	17.4 (11.9-24.7)	14.1 (9.4-20.6)	15.7 (10.3-23.3)	16.7 (11.4-23.8)	14.9 (10.5-20.6)	**Virginia**	20.1 (14.6-27.0)	15.6 (11.1-21.5)	10.9 (8.1-14.7)	10.1 (6.8-14.8)	8.9 (6.2-12.7)
Massachusetts	12.4 (8.2-18.3)	9.9 (7.2-13.5)	10 (6.8-14.5)	10.7 (6.8-16.3)	11.9 (8.3-16.9)	**Washington**	13.4 (9.3-19.0)	14.0 (10.0-19.4)	13.7 (8.4-21.5)	12.9 (9.0-18.2)	12.4 (9.0-16.8)
Michigan	12.9 (10.8-15.4)	11.9 (9.8-14.3)	13 (11.0-15.3)	12.2 (10.0-14.9)	9.5 (7.5-11.9)	**West Virginia**	* (*-*)	14.2 (8.5-22.7)	15.3 (9.9-22.9)	15.3 (9.5-23.6)	16.7 (11.1-24.5)
Minnesota	15.6 (11.5-20.8)	15.5 (11.3-20.8)	9.4 (6.0-14.4)	12.6 (8.0-19.1)	12.5 (8.2-18.8)	**Wisconsin**	* (*-*)	* (*-*)	11.5 (6.9-18.5)	10.3 (6.8-15.5)	14.0 (9.7-19.9)
Mississippi	17.7 (11.9-25.6)	15.7 (10.8-22.3)	18.2 (11.7-27.1)	19.9 (13.0-29.2)	18.6 (14.0-24.3)	**Wyoming**	13.9 (9.8-19.3)	12.0 (7.9-18.0)	10.3 (6.3-16.3)	13.0 (8.3-19.8)	12.0 (7.6-18.3)
Missouri	16.7 (11.7-23.4)	19.2 (12.6-28.1)	14 (8.4-22.6)	12.6 (8.2-18.8)	12.8 (8.8-18.2)						

*Estimates were extracted from "National and State-level Marijuana Trends From 2002–2014" by SAMHSA [https://www.samhsa.gov/samhsa-data-outcomes-quality/major-data-collections/national-state-level-marijuana-trends].

social-economic status, antisocial personality disorder, family history and genetics (Robins 1998; von Sydow et al. 2002; Kendler et al. 2002). Despite multiple known potential causal predictors of cannabis dependence, our understanding on the etiology of cannabis dependence remains limited (van der Pol et al. 2013a; Hindocha et al. 2015).

Genetic topics are attracting increasing focus as variations in cannabis dependence have been observed due to differences in genetic predisposition. Evidence from monozygotic twin and dizygotic twin studies suggests that genetics has played an important role in the development of cannabis dependence (Lynskey et al. 2003; Arpana Agrawal et al. 2004), as well as cannabis use (K. S. Kendler et al. 2002; Kenneth S. Kendler et al. 2015). For example, Kenneth S. Kendler, Myers, and Prescott (2007) studied male-male/female-female twins from the Virginia Twin Registry and estimated the heritability of cannabis dependence. They found that the total heritability for cannabis dependence is 70% and 17% heritability unique to cannabis dependence (after removing heritability shared with cannabis dependence by other influences). Similar findings were found using the Swedish Twin Registry (Kenneth S. Kendler et al. 2015).

As observed in many studies, genetic influences intertwine with other influences (Lynskey et al. 2003; Scherrer et al. 2008). A recent study by (Hines et al. 2018) found that genetic influences share with influences that are due to opportunity of use and to frequency of use. Other studies have found genetic influences shared with cannabis availability and cannabis initiation (A. Agrawal et al. 2005; Gillespie, Neale, and Kendler 2009).

With respect to the pathogenesis of cannabis dependence, conceptual models might help explain the course cannabis dependence, which generally begins with initiation to frequent use and finally to dependence. This progression perspective was first described by (Lee N. Robins 1980) to elucidate the course of drug abuse by studying prospectively the experience of heroin-

using Vietnam soldiers. The course varies depending on the type of drugs due to differences in chemical properties, cost and availability. For example, heroin has high "addictive potential" that first time users rapidly transition to become heroin dependents as compared to first time cannabis users to become cannabis dependents.

Prior research on the natural history of cannabis dependence focused on the emergence of the clinical features of cannabis dependence. For example, Rosenberg and Anthony (2001) investigated the emergence of each clinical feature using the Epidemiologic Catchment Area data and identified the emergence of "desire or fail to control use" as the most occurring clinical feature within roughly 13-15 years of follow-up. Coffey et al. (2002) and Roxburgh et al. (2010) found similar finding in their separate studies in Australia. Dierker et al. (2017) in the US found that the most rapidly emerging clinical feature is "spending more time getting cannabis, using cannabis, or recovering from the effects." The history and clinical course of cannabis dependence is the focus of the third manuscript of this dissertation (see Chapter 5).

2.3.4 Prevention and Control

An increased demand in cannabis dependence treatment is expected as recent changes in cannabis policy in the US result in increased accessibility to cannabis. Currently, an estimated 4.0 million cannabis users experience cannabis use disorder, the majority of whom are individuals age 12-25 (United States 2017b). A recent study conducted by (Marzell, Sahker, and Arndt 2017) reported an increasing first time admissions to treatment for cannabis problems among cannabis users age 20 and younger.

To reduce the risk of cannabis dependence onset, primary preventions need to be in place. Although prevention of drug use also prevents drug dependence, there are tools and interventions that can be used specifically to prevent the onset of use disorders once drug use starts. For

example, the Cannabis Use Problems Identification Test (CUPIT) helps identify cannabis-related problems within the past 12 months through 16 screening questions (Bashford, Flett, and Copeland 2010). Another tool is Cannabis Problems Questionnaire that provides in-depth assessment of cannabis-related problems within the past 3 months (Copeland et al. 2005). Secondary and tertiary preventions are applied to treat and reduce consequences of cannabis dependence, respectively. An example is Cognitive Behavioral Therapy (CBT), which teaches cannabis dependents to identify and change problematic thoughts that triggers cannabis use (McHugh, Hearon, and Otto 2010). A similar approach is used in Relapse Prevention approach. More details about these approaches can be found elsewhere (Guven et al. 2017; Hendershot et al. 2011).

2.4 Prior Studies on Cannabis Dependence with Non-cannabis IRD Use

Several observational studies in the US have indicated that cannabis use might increase the risk of starting to use other illegal drugs (Kandel 1975; Yamaguchi and Kandel 1984; Secades-Villa et al. 2015). This is a transition that potentially is linked by increased 'exposure opportunities' (e.g., greater opportunity to use cocaine for cannabis users compared to non-users) (Wagner and Anthony 2002b). Given opportunity, several influences might account for why some individuals try to use drugs while others do not. For example, Morral, McCaffrey, and Paddock (2002) posit an underlying susceptibility trait such that individuals are more likely to try cannabis and other IRD when given the opportunity. Increased opportunity exposure typically occurs in a social context (Weitzman, Nelson, and Wechsler 2003; Griffin and Botvin 2010) or more generally in low-income neighborhoods (Storr et al. 2004).Others might encounter such opportunity in street markets where cannabis and other illegal drugs are accessible (MacCoun 2011; Reinarman 2009).

A progression of drug use with gradual liberalization of cannabis use might prove to become a major public health concern. One process involves gradually increasing prevalence of cannabis use. Another process involves cannabis users becoming users of other illegal drugs, and if so, they can are more likely to experience adverse cannabis-related outcomes (K. Chen, Kandel, and Davies 1997; Herbeck et al. 2013).

In the case for cannabis dependence, which occurs in approximately 9% of cannabis users irrespective of other IRD use (Wagner and Anthony 2002a), an increasing body of evidence suggests that greater occurrence of dependence was observed among cannabis users who use other drugs. For example, von Sydow et al. (2002) reported in their prospective study in Germany that cannabis users who use other drugs have greater odds of cannabis dependence (OR=4.2, 95% CI = 1.2, 15.0). Similar findings were found by (Lopez-Quintero and Anthony 2015a) in there cross-sectional study. The RR estimates relative to 'cannabis only' users are 4.6 (95% CI = 3.0, 7.1) for cannabis users who use another IRD and 8.7 (95% CI = 5.8, 12.9) for cannabis users who use at least two other IRDs. A more recent study conducted among veterans found that cannabis use disorder increases with the number of drugs used (Bhalla, Stefanovics, and Rosenheck 2017). Another recent study was conducted in Australia among twins and their siblings (Hines et al. 2016). The investigators reported a hazard ratio of 2.1 (95% CI = 1.6, 2.7), comparing the transition from first use to dependence between cannabis users with and without other IRD use.

2.5 Background on Research Approaches in Studies of Cannabis Consequences

2.5.1 Rationale for Cross-Sectional Survey Approach

It can be argued that greater validity can be obtained through prospective research design when investigating the progression of cannabis-related problems and experiences since cannabis onset.

Nevertheless, the design of any cogent prospective and longitudinal study requires a statistical power analysis to detect a difference based on plausible prior estimates of effect sizes, or in this context, an approximation of odds or cumulative incidence ratios, conditional on cannabis involvement. For this reason, this dissertation's reliance upon cross-section ally derived estimates of cannabis involvement makes sense.

2.5.2 Desired Characteristics of a Cross-Sectional Survey Approach

In countries with complete records of all residents, it might be possible to conduct a study based on randomly selected unique identification numbers, allowing to draw a proper statistical survey sample of the population. In countries that never favored the creation of national ID number (e.g., the US), it is necessary to take different approaches, one of which through a multi-stage area probability sampling to sample down to the level of individual respondents. This dissertation research is based on one of the several potential approaches to multi-stage area probability sampling of individuals, as implemented for the US National Surveys on Drug Use and Health.

2.5.3 Participation Levels

Concerns generally arise surrounding certain aspects of prospective designs that potentially reduce validity when used to study sensitive topics (e.g., drug use and dependence). Some concerns pertain to sample attrition when studying 'special populations' (e.g., HIV patients) and response reactivity such that the assessment of drug-related topics changes participants' drug-related behaviors (Jenkins, McAlaney, and McCambridge 2009; J. C. Anthony 2010; McCambridge and Kypri 2011).

In an authoritarian country, all residents of the country might be required to participate in a study (e.g., total population census). In the United States, there are limitations imposed by

ethical principles and regulations that protect human subjects asked to participate in scientific surveys. Here again, a population registry study of all civilian registrants and a mortality follow-up might be conducted without the refinements of informed consents and the difficulties of variation in participation levels. For multi-stage area probability sample surveys in the US, the issue of participation levels must be confronted because not all who are sampled for the surveys will agree to participate. This issue of participation level is an important limitation in US epidemiological research, which is covered in the Discussion sections as a limitation in research of this type.

2.5.4 Assessments

Even with 100% participation, there can be lapses in measurement approaches of several types. At minimum, one hopes for close to 100% reliability as well as 100% accuracy in measurements, and one hopes for no differential measurement errors, as might occur if drug users of one subtype are more or less likely to give reliable or accurate answers to survey questions.

A state of the art approach now involves a departure from the standardized personal interview to assess health characteristics as was used in the first US National Household Surveys on Drug Abuse and in the NIMH Epidemiologic Catchment Area surveys that produce early population-level estimates of drug involvement in US populations. In place of the personal interview, there now is an audio computer-assisted self-interview approach (ACASI). In the ACASI approach, the participant is instructed about use of a computer laptop or tablet keyboard or touchscreen interface, and listens with a headset to the self-interview questions and then keys in the responses, with no involvement of a second party such as an interviewer. The interviewer role has been replaced by the role of a staff member who comes to the dwelling unit with the laptop or tablet, secures informed consent, and then takes basic measurements and provides

instructions about how to use the ACASI apparatus. The respondent then answers the survey questions while the staff member is otherwise occupied (e.g., completing observational assessments or field quality control work on previously completed assessment sessions).

Optimally, every construct under study in research of this type would include multi-item assessment approaches in order to achieve optimal reliability and validity. In actual practice, for cost-efficiency reasons, single item assessments are substituted for the more optimal multi-item approach. Implications in the form of limitations for research of this type are covered in the Discussion chapter of this dissertation report.

2.5.5 Statistical Analysis Approaches

The individual project reports within this dissertation manuscript offer a description of the statistical analysis approaches, but a few preliminary statements might be helpful to readers who are not familiar with epidemiological research of this type. First, due to the multi-stage area probability sampling approach (as opposed to a strictly random sampling approach), the standard formulae for variances and confidence intervals cannot be relied upon. Instead, within a sub-sampled census block group or tract, it must be assumed that sampled participants are more similar to one another than would be the case if participants had been drawn at random from a national registry of civilian residents. Each of the manuscripts described as part of this dissertation project report will include a section that describes how the research approach and statistical analyses have been adapted to deal with these interdependent observations.

Second, the probability sampling in surveys of this type generally involve variations in sample selection probabilities. We can understand these variations most clearly by thinking about a dwelling unit that contains one and only one person eligible for participation. When that is the case, the probability of selecting that person is 100%. Alternatively, consider a dwelling

unit in the sample that contains two potentially eligible participants, and one must be drawn at random. It follows that the probability of selecting one of these two eligible persons is 50%. Then, consider a dwelling unit that has been sampled and within that unit there are three potentially eligible respondents, in which case the probability of selecting that one participant is just 33.3%.

Fundamental principles of survey statistics apply when the goal is to produce estimates of proportions or other summary statistics that hold for the study sample, and these principles generally involve analysis-weighting the observations by the inverse of the selection probabilities. It follows that an analysis-weighting approach generally will help improve estimation for the study population when there is this kind of variation in individual-level or unit-level sampling selection probabilities.

There is an additional issue to be considered in this context when the goal is to produce credible estimates for a national study population. For example, suppose females who are sampled are more likely to participate than males, and all else being equal, after application of analysis-weights, the result is a female-male ratio of 55-to-45, even when it is known from the total population census that the correct values should be 51-to-49. It has become customary to make a correction to the analysis-weighted estimates, via a 'post-stratification adjustment factor' such that the survey-estimated M-F ratio is completely concordant with what is shown in the most recent census value. [One way to think about this post-stratification adjustment is that it (1) compensates for non-response participation levels that are not under the control of the researcher, and (2) makes the survey estimates more credible to some observers than they otherwise might be.]

In this dissertation research project, when estimates are made for the US population, the analysis-weights have been applied, and they take into account both the inverse of the selection probabilities as well as the post-stratification adjustments for age, sex, and race-ethnicity, using US Census Bureau tables as a gold standard. The currently available data do not permit what might be most useful, which is a comparison of inferences when the post-stratification adjustments are applied versus estimates derived when no post-stratification adjustments are applied.

2.5.6 Disregarding Analysis Weights

In both epidemiology and econometrics research, there is a strong tradition in favor of estimation that sets aside the analysis-weights based on inverse of selection probabilities and post-stratification adjustments, particularly when the research goal is causal inference and there is no need to report an estimate that holds for the study population as a whole. Discarding the post-stratification adjustments means that the analysis is based on the data in hand with all its warts, and with no need to assume that non-participants are the same as participants. The issue of non-participation becomes a 'limitation' to be discussed in the research report's Discussion section. Discarding information about selection probabilities at the level of sub-state areas, dwelling units, or individuals might be more controversial, but an argument has been made by the late Professor George Comstock and others (AJE) that causal inference does not require attention to the inverse of selection probabilities. Be that as it may, a useful post-estimation exploratory data analysis can be constructed to address any concern along these lines. That is, for any estimated relationship worth considering, there can be a post-estimation exploratory data analysis that stratifies the observations across an ordinal variable defined in relation to the analysis-weight. Or, in a general or generalized linear model context, product terms can be used to evaluate the

degree to which an overall slope estimate might vary across ordered values of the analysis weight.

2.5.7 Potential Public Health Importance and Significance of this Dissertation Research

Readers might wish to know some details about the potential public health importance and significance of this dissertation research. With respect to potential public health importance, it is possible to echo what has been stated in prior sections of this dissertation research report. Namely, we know a good bit about cannabis effects on human experiences, but we know little about the estimated occurrence of differences in cannabis problem-experiences when cannabis users are studied with and without other post-cannabis onsets of other drugs.

CHAPTER 3: LOWER INCIDENCE OF CANNABIS PROBLEMS WHEN CANNABIS IS THE ONLY DRUG BEING USED? (MANUSCRIPT 1)

Abstract

Lower Incidence of Cannabis Problems When Cannabis Is the Only Drug Being Used?

Aims. In epidemiological estimates for the United States (US), roughly 9%-11% of cannabis users have become cannabis dependent, with apparently lower cumulative incidence of ~2.5% when no other internationally regulated drugs (IRD) have been used. Here, studying newly incident US cannabis users, this study estimates odds of cannabis problem-experiences (PE), and uses odds ratios (OR) to estimate PE associations when 'cannabis only' users add one or more other IRD compounds to the drug-using repertoire, expecting lower PE incidence among those who remain 'cannabis only' users.

Methods. The study population consists of non-institutionalized US residents age 12 and older. Within 11 nationally representative probability samples drawn for the US National Surveys on Drug Use and Health, 2004-2014, the newly incident cannabis users (NICU) with no prior IRD use were identified via computerized self-interview, which also assessed 17 cannabis PE. Among 11838 NICU, 1212 tried 1+ other IRD compounds after cannabis onset but before assessment. Estimated OR are from generalized estimating equations (GEE) logistic regressions, with meta-analysis summaries.

Results. Odds of cannabis-specific problem-experiences, such as 'spending a lot of time' on cannabis-related activities are an estimated 3.0-to-3.5 times greater when 'cannabis only' users add at least one other IRD to the drug-using repertoire ($p<0.05$).

Conclusion. The conclusions are tentative, and raise three especially intriguing questions for polydrug research and possibly for clinical practice. First, "Might cannabis dependence

processes *per se* be slowed or prevented by encouraging newly incident cannabis users to avoid taking other IRD?" Second, “Might this excess risk in the domain of cannabis problems be an example of drug interaction or possibly a signal of host susceptibility?” Third, “Are we seeing an instance of drug-seeking that sometimes follows quickly after onset of a cannabis dependence process?”

3.1 Introduction

This chapter presents this dissertation's first manuscript, which addresses the question of whether "cannabis only" users have different cannabis-related experience compared to polydrug cannabis users. Following this section are the aims states the aims of the research (3.2). The next section (3.3) provides a brief background on cannabis use disorder (CUD) and CUD-related problems and experiences. The fourth section (3.4) details the methodology used to conduct the investigation. The fifth section (3.5) presents the results of the study. Lastly, the sixth section (3.6) provides the discussion, limitation, implication, and conclusion of the study.

3.2 Aim

The main aim is to estimate the excess occurrence of cannabis dependence syndrome-related problems and experiences (PEs) associated with the onset of at least one internationally regulated drug (IRD) soon after cannabis onset. Also, it is this study's aim to produce PE-specific risk estimates to determine which PEs develop rapidly after the onset of cannabis use.

3.3 Background

Globally, cannabis use is becoming more prevalent. In the US, we expect an increase of cannabis use as recent changes in policies lean towards recreational use of cannabis, although the relationship between policy change and cannabis prevalence requires more probing (Wilkinson et al. 2016). Public health impact of the increasing prevalence of cannabis use in the US remains unclear. Cannabis is sometimes considered a "gateway drug" to other internationally regulated drugs in the stages of drug use involvement (Kandel and Faust 1975; Kandel 1975). Opportunity to use drugs might drive the development of these stages (Wagner and Anthony 2002b; Caris et al. 2009). For example, cannabis users are more likely to have exposure to an opportunity to use cocaine (Wagner and Anthony 2002b). While approximately 9% of cannabis users start using an IRD within 2 years after cannabis onset, 44% of cannabis users eventually start using at least one

IRD at one point in their lifetime (Secades-Villa et al. 2015). Our understanding of the interactions of these drugs is very limited even though concurrent use of multiple drugs is the common polydrug phenomenon (Wilkinson et al. 2016).

This study is motivated by the recent findings that users of two or more drugs have greater likelihood of developing drug dependence compared to users of single drug (i.e., cannabis only), and the likelihood doubles for users of three or more drugs (Lopez-Quintero and Anthony 2015b). Irrespective of using other IRDs, an estimated 9%-11% of cannabis users develop a cannabis dependence syndrome (Wagner and Anthony 2002a; Lopez-Quintero et al. 2011). In many research contexts, the number of drugs used is predictive of drug dependence (O'Brien and Anthony 2005; C.-Y. Chen, O'Brien, and Anthony 2005; Lopez-Quintero and Anthony 2015b). Guided by the conceptual model in which the use of other IRD might influence the risk of developing dependence on one drug, this study investigates whether there is an excess risk of cannabis-related PEs associated with the onset of IRD(s) among newly incident cannabis users.

3.4 Methods

3.4.1 Study Population and Design

The United States (US) study population for this work was sampled each year, 2004-2014, for the National Surveys on Drug Use and Health (NSDUH). In each year, Substance Abuse and Mental Health Services Administration (SAMHSA) have drawn, recruited, and assessed nationally representative community survey samples of non-institutionalized civilian US residents age 12 years and older for the NSDUH assessment. These individuals include household residents (those living in houses, townhouses, apartments, condominiums, etc.) and

group quarter residents (those living in shelters, boarding houses, dormitories, etc.). This population covers approximately 97% of the overall US population (Lofquist et al. 2012).

SAMHSA employs multi-stage probability sampling approach to select the nationally representative samples. In each 50 States and District of Columbia, state sampling regions are selected, in which census tracts are chosen. Within the census tracts, census block groups are selected. Segments are then selected within the census block groups. A segment may consist of more than one census block group. Eligible dwelling units are identified for random sampling within area segments. The annual NSDUH samples are non-repeated non-overlapping entities, with participation levels ranging from 70% to 75%. SAMHSA subsamples the data as part of a participant disclosure protection procedure when creating NSDUH public use files, reducing the annual sample size to ~50,000 (United States, 2015).

3.4.2 Study Sample

Aggregated across years, 15896 newly incident cannabis users were identified, of whom 4058 had IRD use prior to the onset of cannabis. This results to the analysis sample of 11,838 newly incident cannabis users, each of whom had no prior IRD use and had started using cannabis for the first time within 12 months before to the survey assessment date (~1000 per survey year). By excluding those with prior IRD, it is possible to estimate the rate of developing cannabis-related PE when one or more IRD use is added after cannabis onset. Figure 3.1 shows a flowchart of selecting the valid analysis sample. These individuals were identified using the self-reported month and year information as described below.

3.4.3 Survey Assessment

NSDUH assessments asked about month and year of newly incident cannabis and other drug use, and included a review of 17 cannabis problems and experiences that had occurred

within a 12-month interval prior to assessment. This information was assembled to identify a group of all newly incident cannabis users with no prior IRD experience, to stratify them by 'cannabis only' status as of the assessment date, and to investigate which, if any, of the 17 cannabis problems and experiences had occurred during the interval after the onset-month of cannabis use and before the month of assessment (i.e., with assessment occurring within 1-12 months after cannabis onset). Net of left-truncation and left-censoring biases that might be quite serious in the study of an IRD such as fentanyl, but less so in this study of cannabis, the resulting estimates provide a forecast of what might be observed in a prospective or longitudinal investigation of newly incident 'cannabis only' users who start extra-medical use of other IRD compounds soon after they first start using cannabis (i.e., within 12 months after 1st cannabis use).

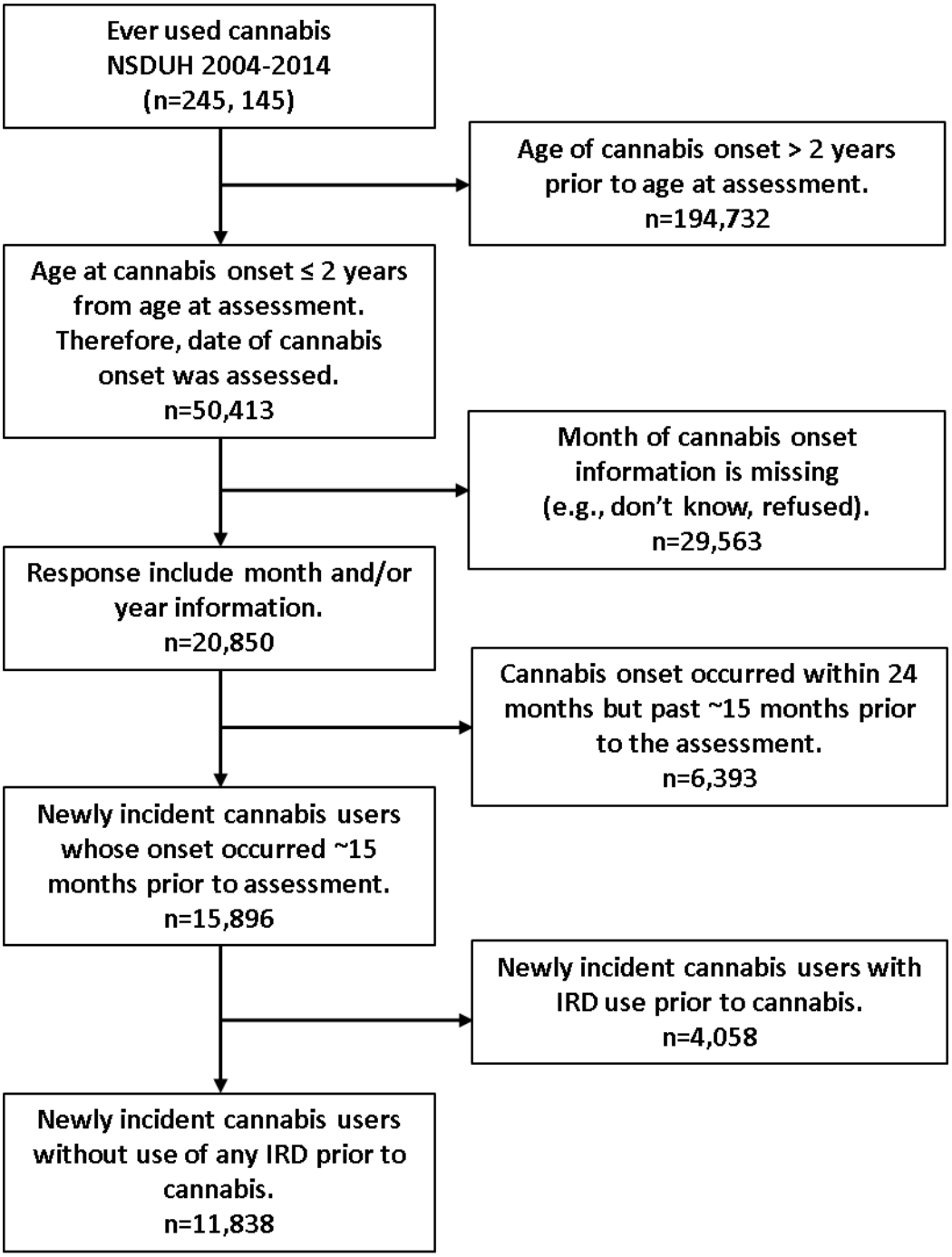
3.4.4 Measures

The key response variable is the first occurrence of 17 individual cannabis use disorder (CUD)-related problems and experiences occurring before the NSDUH assessment date, measured in an ACASI module on CUD. Specific standardized questions are listed in Table 3.1. Several of the questions pertain to the clinical features of DSM-IV cannabis dependence.

The covariate of central interest is onset of use of cannabis plus extra-medical use of at least one other IRD within the 12-month interval, measured via self-reported month and year information of IRD onset. Cannabis use questions were as follows, irrespective of medical or extra-medical use:

- "Have you ever, even once, used marijuana or hashish?"
- "How old were you the first time you used marijuana or hashish?"

Figure 3.1. Flowchart of selecting valid sample. Data are from the National Surveys on Drug Use and Health, 2004-2014 (n=11,838 newly incident cannabis users).



- "Did you first use marijuana or hashish in [CURRENT YEAR-1], or [CURRENT YEAR]?"
- "In what month in [YEAR] did you first use marijuana or hashish?"

Standardized questions on other IRD such as cocaine and opioids were:

- "Did you first use [IRD] in [CURRENT YEAR-1], or [CURRENT YEAR]?"
- "In what month in [YEAR] did you first use [IRD]?"

The answers to these questions were used in order to distinguish "cannabis+IRD" polydrug users from "cannabis only" users. In this study, the cannabis+IRD polydrug users are newly incident cannabis users who started extra-medical use of one or more of the following IRD after cannabis onset: cocaine, crack cocaine, methamphetamine, other 'stimulants,' heroin, OxyContin, other 'prescription pain relievers' (generally opioids)**,** **'**inhalants,' 'sedative-hypnotics,' 'PCP,' 'hallucinogens,' 'LSD,' 'ecstasy,' and 'tranquilizers' (i.e., anxiolytic products). That is, during the 1-12-month interval between 1st cannabis use and the assessment date, this study's 'cannabis only' users had not started extra-medical use of these other IRD, whereas 'cannabis+IRD polydrug' users had done so.

Other covariates taken into account were measured by standardized questions in other NSDUH assessment modules. They included age, sex, and ethnic self-identification ('race-ethnicity'). Whether the users had consumed alcoholic beverages or tobacco/nicotine products also was considered, but other covariates were deemed potential consequences of newly incident drug use (e.g., schooling; being unemployed; income) and have not been taken into account in order to avoid model mis-specification errors for estimation of odds ratios.

Table 3.1. CUD-associated Problems and Experiences Assessment Questions from the National Survey on Drug Use and Health Cannabis Use Module.*

1. During the past 12 months, was there a month or more when you spent a lot of your time getting or using marijuana or hashish?
2. During the past 12 months, was there a month or more when you spent a lot of your time getting over the effects of the marijuana or hashish you used?
3. Were you able to keep to the limits you set, or did you often use marijuana or hashish more than you intended to?
4. During the past 12 months, did you need to use more marijuana or hashish than you used to in order to get the effect you wanted?
5. During the past 12 months, did you notice that using the same amount of marijuana or hashish had less effect on you than it used to?
6. During the past 12 months, did you want to or try to cut down or stop using marijuana or hashish?
7. During the past 12 months, were you able to cut down or stop using marijuana or hashish every time you wanted to or tried to?
8. During the past 12 months, did you have any problems with your emotions, nerves, or mental health that were probably caused or made worse by your use of marijuana or hashish?
9. Did you continue to use marijuana or hashish even though you thought it was causing you to have problems with your emotions, nerves, or mental health?
10. During the past 12 months, did you have any physical health problems that were probably caused or made worse by your use of marijuana or hashish?
11. Did you continue to use marijuana or hashish even though you thought it was causing you to have physical problems?
12. During the past 12 months, did using marijuana or hashish cause you to give up or spend less time doing these types of important activities?
13. During the past 12 months, did using marijuana or hashish cause you to have serious problems like this either at home, work, or school?
14. During the past 12 months, did you regularly use marijuana or hashish and then do something where using marijuana or hashish might have put you in physical danger?
15. During the past 12 months, did using marijuana or hashish cause you to do things that repeatedly got you in trouble with the law?
16. During the past 12 months, did you have any problems with family or friends that were probably caused by your use of marijuana or hashish?
17. Did you continue to use marijuana or hashish even though you thought it caused problems with family or friends?

*There is an NSDUH measurement assumption that the listed cannabis problems and experiences do not occur unless the newly incident user has consumed cannabis on at least six occasions since onset of cannabis use (or within the 12-month interval prior to assessment).

3.4.5 Statistical Analyses

The study estimates included analysis-weighted incidence proportions for each of the 17 cannabis PE and for cannabis dependence among newly incident cannabis users considered as a group and stratified by 'cannabis only' status, as well as analysis-weighted odds ratio (OR) estimates that convey the degree to which incidence of the PE might be lower for 'cannabis only' users observed within 1-12 months after first cannabis use. Due to statistical interdependence of the 17 PE, OR estimation is from a generalized linear model with a logistic link function and the generalized estimating equations (GZLM/GEE) of Liang and Zeger (1986), with and without covariates taken into account. Model specifications included 'robust' variance estimation algorithms of the Stata Version 14 statistical software (StataCorp. 2015).

Estimates were formed for each of the 11 survey years, with treatment of each year's sample as if it were a statistically independent sample of the US population experience, or a 'virtual replication' as defined by Finifter (1972). Thereafter, to summarize across the 11 virtual replications, meta-analysis approach was used, also with Stata software.

In an initial GZLM/GEE step, the multivariate response model framework was used to produce a common slope estimate – i.e.., with borrowing of information across all 17 CUD-associated PE. In subsequent analysis steps, the model was re-specified to produce slope estimates for each cannabis PE. (The OR is the slope after exponentiation.)

In post-estimation exploratory data analysis steps, some evidence of possible subgroup variation in the GZLM/GEE slope estimates was found. This evidence was presented for subgroups defined by elapsed time since cannabis onset. For a final post-estimation exploratory data analysis, a mis-specified model was constructed, taking into account how frequently cannabis had been consumed since first use, as measured by one of these NSDUH questions:

Table 3.2. Characteristics of the study sample. Data are from the US National Survey on Drug Use and Health, 2004-2014 (n=11,838).

(a) Cannabis only (n = 10,626)												
	NSDUH Year											
	2004	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**Total**
n	833	820	818	910	872	1077	1071	1171	1084	1104	866	10622
Age[a]												
12-17	541	533	532	588	525	646	661	707	653	666	528	6580
18-25	274	276	273	306	332	420	394	439	410	414	302	3840
26+	18	11	13	16	15	11	16	25	21	24	36	206
Sex												
Males	367	404	410	444	432	565	561	598	518	482	422	5203
Females	466	416	408	466	440	512	510	573	566	622	444	5423
Ethnic Self-Identification[b]												
NH Whites	544	514	493	566	557	642	629	710	613	618	483	6369
NH Blacks	134	137	146	135	121	162	168	166	171	170	118	1628
NH Nat. Amer.	12	8	13	12	14	15	19	12	12	9	14	140
NH Nat. Haw.	1	10	2	1	4	4	7	5	1	9	4	48
NH Asian	24	19	21	30	22	32	29	31	37	51	34	330
NH >1 group	24	23	29	33	28	55	45	68	54	56	47	462
Hispanic	94	109	114	133	126	167	174	179	196	191	166	1649
Alcohol Use												
Never Used	76	77	60	84	84	114	126	168	144	179	160	1272
Ever Used	757	743	758	826	788	963	945	1,003	940	925	706	9354
Tobacco Smoking												
Never Used	257	256	263	339	300	420	444	528	552	609	509	4477
Ever Used	576	564	555	571	572	657	627	643	532	495	357	6149

Table 3.2 (cont'd)

(b) Cannabis with IRD (n = 1212)												
	NSDUH Year											
	2004	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**Total**
n	122	130	108	108	125	139	124	127	93	78	58	1212
Age[a]												
12-17	88	101	77	70	87	91	98	90	67	52	38	859
18-25	33	28	28	37	38	48	25	37	26	26	18	344
26+	1	1	3	1	0	0	1	0	0	0	2	9
Sex												
Males	52	62	46	52	56	72	67	68	46	37	28	586
Females	70	68	62	56	69	67	57	59	47	41	30	626
Ethnic Self-Identification[b]												
NH Whites	96	99	82	80	90	96	80	88	60	49	39	859
NH Blacks	10	3	4	4	8	6	9	5	8	5	5	67
NH Nat. Amer.	4	1	1	2	1	1	2	0	0	3	1	16
NH Nat. Haw.	1	0	0	0	0	1	0	0	1	0	0	3
NH Asian	2	0	6	5	3	2	2	3	1	1	0	25
NH >1 group	3	7	3	4	7	7	6	5	2	4	5	53
Hispanic	6	20	12	13	16	26	25	26	21	16	8	189
Alcohol Use												
Never Used	7	5	8	5	6	9	3	12	7	6	3	71
Ever Used	115	125	100	103	119	130	121	115	86	72	55	1141
Tobacco Smoking												
Never Used	22	20	15	18	27	31	30	36	31	27	22	279
Ever Used	100	110	93	90	98	108	94	91	62	51	36	933

[a]Age categories in analysis were 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22-23, 24-25, 26-29, 30-34, 35-49, 50-64, 65+.

[b] NH = Non-Hispanic; Nat. Amer = Native American; Nat. Haw. = Native Hawaiian.

Table 3.3. Estimated relationship between the onset of internationally regulated drugs (IRD) soon after cannabis onset and developing CUD-associated problems and experiences, based upon a common slope model. Also, meta-analytic summary estimates are presented. Data are from the US National Survey on Drug Use and Health, 2004-2014, (n=11,838).

	Unweighted OR (95% CI)	Unweighted aOR[a] (95% CI)	Weighted OR (95% CI)	Weighted aOR[a] (95% CI)
2004	3.2 (2.4, 4.3)	3.3 (2.4, 4.5)	3.6 (2.4, 5.3)	3.7 (2.4, 5.6)
2005	2.7 (2.0, 3.8)	3.2 (2.3, 4.6)	3.4 (2.2, 5.3)	3.6 (2.4, 5.4)
2006	2.0 (1.5, 2.7)	2.3 (1.6, 3.4)	2.3 (1.4, 3.8)	3.1 (1.8, 5.1)
2007	3.8 (2.8, 5.2)	3.9 (2.7, 5.4)	5.1 (3.3, 7.8)	5.3 (3.3, 8.5)
2008	3.7 (2.7, 4.9)	4.0 (3.0, 5.5)	4.0 (2.8, 5.7)	3.5 (2.4, 5.1)
2009	2.7 (2.0, 3.6)	2.4 (1.7, 3.3)	2.8 (1.9, 4.2)	2.6 (1.6, 4.0)
2010	3.1 (2.3, 4.1)	3.0 (2.2, 4.2)	2.9 (1.9, 4.3)	3.1 (1.9, 5.0)
2011	2.9 (2.2, 3.9)	3.0 (2.2, 4.1)	2.9 (2.0, 4.1)	2.7 (1.8, 3.9)
2012	3.0 (2.2, 4.1)	3.2 (2.2, 4.6)	2.7 (1.7, 4.5)	2.1 (1.3, 3.6)
2013	3.1 (2.2, 4.5)	3.2 (2.1, 4.8)	3.4 (2.1, 5.5)	3.7 (2.1, 6.6)
2014	4.0 (2.7, 5.8)	3.6 (2.4, 5.6)	5.0 (2.6, 9.6)	3.9 (2.1, 7.1)
Meta-analytic summary	3.1 (2.7, 3.4)*	3.2 (2.8, 3.5)*	3.3 (2.9, 3.8)	3.3 (2.9, 3.8)

OR = Odds Ratio; aOR = Adjusted Odds Ratio; 95% CI = 95% Confidence Interval

[a] Adjusted for age, sex, ethnic self-identification, lifetime alcohol use, and lifetime tobacco use.

*When analysis weights are applied, these meta-analytic summary estimates are 3.3 (95% CI = 2.9, 3.8) and 3.3 (95% CI = 2.9, 3.8), with and without covariate adjustment, respectively.

"On how many days in the past 12 months did you use marijuana or hashish?" "On average, how many days did you use marijuana or hashish each month during the past 12 months?" or "On average, how many days did you use marijuana or hashish each week during the past 12 months?"

3.5 Results

Table 3.2a and Table 3.2b provide year-by-year description of the study sample, with unweighted numbers of newly incident cannabis users in a range from 924 to 1182, for 'cannabis only' users and 'cannabis+IRD' users, respectively. A majority of the newly incident cannabis users in the sample were age 12-17 years; virtually all had previously consumed alcohol, and

many had used tobacco products. Slightly more than 80% of the newly incident cannabis users remained 'cannabis only' users at assessment; there were 1212 'cannabis+IRD' polydrug users.

Rank-ordered by frequency of occurrence during the 1-12-month interval between 1st cannabis use and assessment, the cannabis problem-experiences were: "Wanted/Tried to cut down or stop using cannabis" (22%), "Spent a lot of time getting or using cannabis" (12%), "Needed more to get the same effect" (7%), "Caused problems with family or friends" (5%), "Used the same amount but had less effect" (5%), "Spent less time doing important activities" (4%), "Used cannabis and did dangerous activities" (4%), "Caused serious problem at home or work or school" (4%), "Caused problems with emotions" (4%), "Continued use despite problems with family or friends" (3%), "Was not able to keep limits" (2%), "Continued use despite emotional problems" (2%), "Was not able to cut or stop" (2%), "Spent a lot of time getting over effects" (1%), "Caused repeated problems with the law" (1%), "Caused physical problems" (1%), and "Continued use despite physical problems" (<1%) (data not shown in a table; available upon request).

Table 3.3 shows the OR estimates and meta-analytic summary estimates, which generally convey an excess occurrence of cannabis PE for the subgroup of 'cannabis only' users who have added at least one other IRD to the drug-using repertoire. The OR estimates vary somewhat year-by-year across the 11 'virtual replications,' but generally show excess occurrence of cannabis PE among the polydrug cannabis users (meta-analytic summary OR estimate = 3.1; 95% CI = 2.7, 3.4). After covariate adjustment, this meta-analytic summary estimate is 3.3 (95% CI = 2.9, 3.8). Similar OR estimates can be seen with and without application of analysis weights. An exploratory analysis shows that similar findings are observed for the relationship between polydrug cannabis use and DSM-IV cannabis dependence (Table 3.4).

Table 3.4. Meta-analytic summary of year-by-year estimates of the relationship between the onset of internationally regulated drugs (IRD) soon after cannabis onset and developing DSM-IV cannabis dependence. Data are from the US National Survey on Drug Use and Health, 2004-2014, n=11,838. Proportions of DSM-IV cannabis dependents among newly incident cannabis users after pooling the 11 NSDUH samples are 0.13 and 0.03 for cannabis+IRD users and cannabis only users, respectively.[*]

	Unweighted OR (95% CI)	Unweighted aOR[a] (95% CI)	Weighted OR (95% CI)	Weighted aOR[a] (95% CI)
2004	7.8 (4.0,15.5)	7.3 (3.5,15.2)	6.8 (2.8,16.5)	5.7 (2.4,13.6)
2005	5.1 (2.5,10.4)	4.5 (2.1, 9.8)	7.1 (2.8,17.9)	5.1 (2.1,11.9)
2006	2.1 (0.9, 4.7)	2.5 (1.1, 5.9)	2.4 (0.8, 6.6)	3.2 (1.1, 9.4)
2007	7.3 (3.9,13.6)	6.3 (3.2,12.3)	11.3 (5.0,25.8)	9.0 (3.8,21.4)
2008	9.0 (4.5,17.9)	8.2 (4.0,16.9)	8.6 (3.7,20.0)	7.4 (3.2,17.1)
2009	3.6 (1.9, 6.8)	3.1 (1.6, 6.0)	4.7 (1.7,12.5)	4.3 (1.6,11.3)
2010	5.3 (2.8,10.1)	3.6 (1.8, 7.3)	5.4 (2.3,13.0)	3.4 (1.5, 7.9)
2011	3.3 (1.7, 6.5)	2.5 (1.2, 5.1)	3.0 (1.2, 7.2)	1.9 (0.8, 4.6)
2012	3.3 (1.5, 7.4)	3.0 (1.3, 7.0)	3.5 (1.0,11.7)	2.4 (0.6, 8.7)
2013	8.2 (3.9,17.1)	7.5 (3.5,16.1)	9.0 (3.2,25.7)	8.0 (2.7,23.5)
2014	17.1 (7.4,39.6)	13.1 (5.2,32.6)	30.7(10.2,92.5)	26.1 (8.6,79.2)
Meta-analytic summary	5.6 (4.5, 6.9)	4.8 (3.8, 6.0)	6.5 (4.9, 8.6)	5.2 (3.9, 6.9)

OR = Odds Ratio; aOR = Adjusted Odds Ratio; 95% CI = 95% Confidence Interval.

[*] Cross-tabulation results: Cannabis only (277/10349); cannabis+IRD (153/1212).

[a] Adjusted for age, sex, ethnic self-identification, lifetime alcohol use, and lifetime tobacco use.

Table 3.5 shows the PE-specific year-by-year OR estimates and meta-analytic summary estimates, with excess occurrence of every cannabis PE among polydrug cannabis users (see unweighted OR estimates; Table 3.5). After covariate adjustment, similar results were observed (see unweighted aOR estimates; Table 3.5). With and without covariate adjustment, the strongest association was observed for "Spent a lot of time getting or using cannabis." When weighted to the population without covariate adjustment, the results remained statistically robust (see weighted OR estimates; Table 3.5). With covariate adjustment, the difference between the two groups was not statistically robust in four of the PEs, namely "Used the same amount but had

Table 3.5. Meta-analytic summary estimates of the relationship between the onset of internationally regulated drugs (IRD) soon after cannabis onset and developing specific PE, based upon PE-specific slope approach. Data are from the US National Survey on Drug Use and Health, 2004-2014 (n=11,838).

Cannabis Problems and Experience	Unweighted OR (95% CI)	Unweighted aOR[a] (95% CI)	Weighted OR (95% CI)	Weighted aOR[a] (95% CI)
Wanted/Tried to cut down or stop using cannabis	2.1 (1.9, 2.4)	2.0 (1.7, 2.2)	2.4 (2.0, 2.9)	2.1 (1.8, 2.5)
Spent a lot of time getting or using cannabis	5.1 (4.5, 5.9)	4.9 (4.3, 5.6)	5.0 (4.2, 6.0)	4.5 (3.7, 5.4)
Needed more to get the same effect	4.6 (3.8, 5.5)	4.3 (3.6, 5.1)	5.3 (4.2, 6.7)	4.7 (3.7, 6.0)
Caused problems with family or friends	3.7 (2.9, 4.7)	3.4 (2.7, 4.3)	4.3 (3.1, 5.9)	3.8 (2.8, 5.0)
Spent less time doing important activities	4.4 (3.5, 5.7)	4.1 (3.3, 5.2)	4.6 (3.5, 6.1)	4.0 (3.0, 5.3)
Contd. use despite problems w/ family or friends[b]	4.7 (3.5, 6.2)	4.3 (3.3, 5.6)	4.7 (2.9, 7.6)	4.1 (2.7, 6.3)
Used cannabis and did dangerous activities	4.0 (3.1, 5.3)	3.8 (2.9, 4.9)	3.4 (2.2, 5.3)	3.0 (1.9, 4.7)
Used the same amount but had less effect	1.7 (1.4, 2.2)	1.6 (1.3, 2.0)	1.4(>1.0,2.0)	1.2 (0.9, 1.7)
Caused serious problem at home or work or school	3.9 (3.1, 5.1)	3.6 (2.8, 4.6)	4.3 (2.9, 6.4)	3.8 (2.6, 5.5)
Was not able to keep limits	4.4 (3.2, 6.0)	4.0 (2.9, 5.6)	5.1 (3.3, 7.7)	4.5 (3.0, 6.7)
Caused problems with emotions	3.0 (2.4, 3.7)	2.8 (2.2, 3.4)	3.8 (2.8, 5.2)	3.3 (2.4, 4.5)
Contd. use despite emotional problems[c]	3.9 (2.9, 5.2)	3.5 (2.6, 4.7)	4.6 (3.0, 7.1)	4.0 (2.7, 5.9)
Spent a lot of time getting over effects	1.7 (1.2, 2.5)	1.5(>1.0,2.2)	1.7(>1.0,2.7)	1.4 (0.9, 2.3)
Caused repeated problems with the law	4.8 (3.2, 7.2)	4.3 (2.9, 6.4)	4.6 (2.4, 8.8)	3.9 (2.0, 7.6)
Contd. use despite physical problems[d]	2.5 (1.8, 3.6)	2.6 (1.8, 3.7)	2.3 (1.1, 4.9)	2.0(<1.0,4.2)
Was not able to cut or stop[e]	3.6 (2.4, 5.4)	3.3 (2.3, 4.9)	4.3 (2.7, 6.8)	3.7 (2.4, 5.8)
Caused physical problems	2.3 (1.5, 3.7)	2.2 (1.4, 3.3)	2.2(>1.0,4.5)	1.9 (0.9, 3.9)

OR = Odds Ratio; aOR = Adjusted Odds Ratio; 95% CI = 95% Confidence Interval
[a] Adjusted for age, sex, ethnic self-identification, lifetime alcohol use, and lifetime tobacco use.
[b] Conditional on the positive response to the PE, "Caused physical problems."
[c] Conditional on the positive response to the PE, "Caused problems with emotions."
[d] Conditional on the positive response to the PE, "Caused physical problems."
[e] Conditional on the positive response to the PE, "Wanted/Tried to cut down or stop using cannabis."

less effect," "Spent a lot of time getting over effects," "Continued use despite physical problems," and "Caused physical problems" (see weighted aOR estimates; Table 3.5). With and without covariate adjustment, the strongest association was for "Needed more to get the same effect."

Table 3.6 and Table 3.7 show post-estimation results of stratified analyses based on timing of cannabis onset and frequency of cannabis use, respectively. After stratification based on the timing of cannabis onset, the findings were similar to our main findings (Table 3.6).

Table 3.6. Estimated relationship between the onset of internationally regulated drugs (IRD) soon after cannabis onset and developing CUD-associated problems and experiences based on the timing of cannabis onset within 12 months before assessment.* Data are from the US National Survey on Drug Use and Health, 2004-2014, (n=11,838).

	Unweighted OR (95% CI)	Unweighted aOR[a] (95% CI)	Weighted OR (95% CI)	Weighted aOR[a] (95% CI)
Month 1-6	2.5 (2.1, 2.8)	2.5 (2.2, 2.8)	2.6 (2.2, 3.2)	2.5 (2.1, 3.0)
Month 7-12	3.4 (2.7, 4.1)	3.3 (2.7, 4.1)	3.7 (2.8, 4.9)	3.7 (2.8, 5.0)

OR = Odds Ratio; aOR = Adjusted Odds Ratio; 95% CI = 95% Confidence Interval
*Timing of cannabis onset categories: Month 1-6 (e.g., January-June of current year if assessment was quarter 3 of current year); Month 7-12 (e.g., August-December of prior year if assessment was quarter 3 of current year).

Excess occurrence of cannabis PE was observed among polydrug cannabis users, with higher point estimates among those whose cannabis onset occurred within 6 months prior to the assessment. Similarly, the findings from the stratified analysis based on the frequency of cannabis use (monthly, weekly, and daily) did not vary from the overall findings (Table 3.7). Point estimates tended to be higher among monthly users of cannabis. The PE-specific meta-analytic summary estimates from post-estimation stratified analyses based on the timing of cannabis onset and frequency of cannabis use are presented in Table 3.8 (a-b) and Table 3.9, respectively. To further investigate whether there might be other factors that might explain the observed association, an analysis was conducted to test possible measurement invariance between newly incident cannabis users whose onset occurred during months 1-6 and months 7-12 (Figure 2 for the conceptual model). No difference was found between the two timing groups. Detailed results can be found in Appendix A. In addition, covariation of the pairs of PE among the newly incident cannabis users within the 12-month interval are presented in Table 3.10.

Table 3.7. Estimated relationship between the onset of internationally regulated drugs (IRD) soon after cannabis onset and developing CUD-associated problems and experiences based upon the frequency of cannabis use. Data are from the US National Survey on Drug Use and Health, 2004-2014, (n=11,838).

	Unweighted OR (95% CI)	Unweighted aOR[a] (95% CI)	Weighted OR (95% CI)	Weighted aOR[a] (95% CI)
Monthly[a]	2.7 (2.3, 3.2)	2.8 (2.3, 3.4)	2.8 (2.1, 3.5)	2.7 (1.9, 3.7)
Weekly[b]	1.7 (1.5, 1,9)	1.9 (1.6, 2.2)	1.8 (1.5, 2.1)	1.9 (1.6, 2.3)
Daily[c]	1.9 (1.5, 2.3)	2.5 (1.8, 3.4)	1.7 (1.3, 2.2)	2.5 (1.7, 3.6)

OR = Odds Ratio; aOR = Adjusted Odds Ratio; 95% CI = 95% Confidence Interval
[a] Monthly group includes cannabis users who used cannabis at least six times but less than 12 times a year, and those who used cannabis less than 4 times a month.
[b] Weekly group includes cannabis users who used cannabis 1-4 days a week, more than 48 days but less 260 days a year, and more than 2 days a month but less than 24 days a month.
[c] Daily group includes cannabis users who used cannabis more than 4 days a week, more than 259 days a year, and more than 23 days a month.

3.6 Discussion and Conclusion

Several findings from this research are worth noting. First, this study found evidence of the relationship between onset of IRD soon after cannabis onset and the development of CUD-associated PEs. Cannabis+IRD polydrug users have excess odds of developing CUD-associated PEs compared to cannabis only users. These findings did not vary after accounting for the timing of cannabis onset and the frequency of cannabis use. Second, cannabis+IRD polydrug users developed all PEs more rapidly compared to cannabis only users. After covariate adjustment, 13 PEs had robust association. Third, this study found that the strongest association was for "spent a lot of time getting or using cannabis" when using the sample data. Weighted to the US population, the strongest association was for "needed more to get the same effect."

Table 3.8. Meta-analytic summary estimates of the relationship between the onset of internationally regulated drugs soon after cannabis onset and developing specific PE using a PE-specific slope approach, based on the timing of cannabis onset. Data are from the US National Survey on Drug Use and Health, 2004-2014 (n=11,838).

(a) First 6 months

Cannabis Problems and Experience	Unweighted OR (95% CI)	Unweighted aOR[a] (95% CI)	Weighted OR (95% CI)	Weighted aOR[a] (95% CI)
Wanted/Tried to cut down or stop using cannabis	1.6 (1.4, 1.9)	1.4 (1.2, 1.7)	1.8 (1.4, 2.2)	1.5 (1.2, 1.8)
Spent a lot of time getting or using cannabis	4.2 (3.3, 5.2)	3.8 (3.1, 4.7)	4.1 (3.3, 5.1)	3.5 (2.8, 4.4)
Needed more to get the same effect	3.8 (3.0, 4.9)	3.5 (2.8, 4.3)	4.3 (3.1, 5.9)	3.7 (2.7, 5.0)
Caused problems with family or friends	2.9 (2.2, 3.9)	2.7 (2.1, 3.4)	3.5 (2.4, 5.0)	2.9 (2.0, 4.1)
Spent less time doing important activities	3.6 (2.7, 4.9)	3.3 (2.4, 4.4)	3.6 (2.6, 5.1)	3.0 (2.2, 4.2)
Contd. use despite problems w/ family or friends[b]	3.5 (2.6, 4.7)	3.1 (2.3, 4.2)	3.5 (2.2, 5.5)	2.9 (1.9, 4.5)
Used cannabis and did dangerous activities	3.3 (2.5, 4.4)	3.0 (2.3, 3.9)	2.7 (1.7, 4.4)	2.3 (1.4, 3.7)
Used the same amount but had less effect	1.6 (1.2, 2.1)	1.4 (1.1, 1.9)	1.4 (0.9, 2.1)	1.1 (0.7, 1.6)
Caused serious problem at home or work or school	2.9 (2.2, 3.8)	2.6 (1.9, 3.4)	3.0 (1.8, 4.9)	2.4 (1.5, 4.0)
Was not able to keep limits	3.1 (2.1, 4.7)	2.8 (1.9, 4.2)	3.3 (2.0, 5.3)	2.8 (1.7, 4.4)
Caused problems with emotions	2.3 (1.8, 3.1)	2.1 (1.6, 2.8)	2.4 (1.4, 4.1)	2.0 (1.2, 3.3)
Contd. use despite emotional problems[c]	3.1 (2.2, 4.5)	2.8 (1.9, 4.0)	2.6 (1.5, 4.8)	2.2 (1.3, 3.8)
Spent a lot of time getting over effects	1.6 (1.3, 2.0)	1.4 (1.1, 1.8)	1.8 (1.3, 2.4)	1.5 (1.1, 2.0)
Caused repeated problems with the law	3.3 (2.1, 5.2)	2.9 (1.9, 4.5)	3.1 (1.5, 6.4)	2.6 (1.3, 5.1)
Contd. use despite physical problems[d]	4.0 (1.9, 8.5)	2.4 (1.4, 4.2)	4.0 (1.5,10.6)	2.2 (<1.0,5.0)
Was not able to cut or stop[e]	2.9 (1.9, 4.5)	2.6 (1.7, 4.0)	2.9 (1.7, 5.0)	2.4 (1.4, 4.1)
Caused physical problems	1.9 (1.3, 2.9)	1.7 (1.1, 2.6)	1.9 (>1.0,3.4)	1.5 (0.8, 2.9)

Table 3.8 (cont'd)

(b) Second 6 months

Cannabis Problems and Experience	Unweighted OR (95% CI)	Unweighted aOR[a] (95% CI)	Weighted OR (95% CI)	Weighted aOR[a] (95% CI)
Wanted/Tried to cut down or stop using cannabis	2.5 (2.0, 3.2)	2.4 (1.9, 3.1)	3.0 (2.2, 4.0)	2.8 (1.9, 4.1)
Spent a lot of time getting or using cannabis	4.8 (3.6, 6.3)	4.7 (3.5, 6.2)	4.6 (3.2, 6.5)	4.5 (3.1, 6.5)
Needed more to get the same effect	4.2 (2.9, 6.1)	4.0 (2.6, 6.2)	4.3 (2.6, 7.3)	4.0 (2.2, 7.2)
Caused problems with family or friends	4.4 (3.0, 6.3)	4.2 (2.8, 6.1)	4.0 (2.5, 6.5)	3.6 (2.2, 5.7)
Spent less time doing important activities	5.2 (3.6, 7.6)	4.9 (3.4, 7.3)	4.7 (3.0, 7.6)	4.5 (2.8, 7.3)
Contd. use despite problems w/ family or friends[b]	6.6 (3.8,11.3)	6.2 (3.5,11.0)	5.1 (2.2,12.1)	4.8 (2.1,10.8)
Used cannabis and did dangerous activities	4.2 (2.8, 6.4)	4.0 (2.7, 6.1)	3.6 (2.0, 6.4)	3.3 (1.9, 5.6)
Used the same amount but had less effect	2.3 (1.7, 3.1)	2.3 (1.6, 3.2)	2.7 (1.8, 3.9)	2.7 (1.8, 4.3)
Caused serious problem at home or work or school	5.5 (3.8, 7.9)	5.3 (3.6, 7.7)	6.0 (3.8, 9.6)	6.0 (3.8, 9.5)
Was not able to keep limits	4.6 (2.6, 8.1)	4.5 (2.6, 7.8)	5.4 (2.5,11.5)	5.2 (2.4,11.3)
Caused problems with emotions	4.2 (2.8, 6.3)	4.0 (2.7, 6.1)	5.5 (3.3, 9.1)	5.0 (3.0, 8.5)
Contd. use despite emotional problems[c]	4.7 (3.0, 7.3)	4.4 (2.7, 7.0)	5.3 (2.8,10.1)	4.8 (2.6, 8.9)
Spent a lot of time getting over effects	2.5 (1.9, 3.5)	2.5 (1.8, 3.5)	3.0 (1.9, 4.7)	3.1 (1.9, s5.0)
Caused repeated problems with the law	3.9 (2.4, 6.3)	3.7 (2.3, 5.8)	6.1 (2.4,15.8)	6.0 (2.3,15.2)
Contd. use despite physical problems[d]	2.7 (2.0, 3.7)	2.7 (2.0, 3.7)	2.7 (1.9, 3.9)	2.5 (1.7, 3.8)
Was not able to cut or stop[e]	4.0 (2.5, 6.5)	3.9 (2.4, 6.2)	5.3 (2.7,10.4)	5.2 (2.7,10.2)
Caused physical problems	2.9 (2.1, 4.1)	2.9 (2.1, 4.0)	3.1 (2.0, 4.8)	3.0 (1.7, 5.1)

OR = Odds Ratio; aOR = Adjusted Odds Ratio; 95% CI = 95% Confidence Interval

[a] Adjusted for age, sex, ethnic self-identification, lifetime alcohol use, and lifetime tobacco use.

[b] Conditional on the positive response to the PE, "Caused physical problems."

[c] Conditional on the positive response to the PE, "Caused problems with emotions."

[d] Conditional on the positive response to the PE, "Caused physical problems."

[e] Conditional on the positive response to the PE, "Wanted/Tried to cut down or stop using cannabis."

Table 3.9. Meta-analytic summary of year-by-year weighted crude estimates of the relationship between the onset of internationally regulated drugs soon after cannabis onset and developing specific PE, based upon PE-specific slope approach. Data are from the US National Survey on Drug Use and Health, 2004-2014 (n=11,838).

Cannabis Problems and Experience	Monthly aOR (95% CI)	Weekly aOR (95% CI)	Daily aOR (95% CI)
Wanted/Tried to cut down or stop using cannabis	*NTS*	7.9 (6.8, 9.1)	2.1 (1.6, 3.0)
Spent a lot of time getting or using cannabis	11.0 (6.8,17.7)	11.0 (8.4,14.4)	*NTS*
Needed more to get the same effect	10.4 (3.9,27.4)	11.5 (8.3,15.9)	11.0 (7.4,16.3)
Caused problems with family or friends	9.5 (4.6,19.5)	5.9 (4.6, 7.5)	4.6 (3.1, 6.8)
Spent less time doing important activities	9.8 (5.1,18.8)	6.9 (5.2, 9.2)	7.1 (4.8,10.6)
Contd. use despite problems w/ family or friends[b]	6.7 (3.3,13.9)	7.4 (5.1,10.7)	6.2 (4.0, 9.6)
Used cannabis and did dangerous activities	*NTS*	6.1 (4.6, 8.1)	3.1 (1.6, 5.9)
Used the same amount but had less effect	7.8 (3.7,16.3)	5.8 (4.3, 7.6)	1.9 (1.1, 3.4)
Caused serious problem at home or work or school	*NTS*	7.8 (5.8,10.6)	5.5 (3.6, 8.5)
Was not able to keep limits	3.4 (1.2, 9.8)	9.3 (6.0,14.3)	5.4 (3.3, 8.8)
Caused problems with emotions	*NTS*	5.2 (3.7, 7.3)	2.6 (1.6, 4.0)
Contd. use despite emotional problems[c]	*NTS*	7.4 (4.8,11.4)	3.6 (2.3, 5.8)
Spent a lot of time getting over effects	*NTS*	6.4 (4.0,10.0)	1.9 (1.1, 3.2)
Caused repeated problems with the law	*NTS*	10.6 (3.8,29.8)	5.6 (2.5,12.8)
Contd. use despite physical problems[d]	*NTS*	*NTS*	3.9 (2.2, 6.8)
Was not able to cut or stop[e]	*NTS*	6.8 (3.7,12.6)	4.4 (2.0, 9.7)
Caused physical problems	4.5 (1.7,11.8)	5.5 (3.0,10.1)	2.4 (1.4, 3.9)

aOR = Adjusted Odds Ratio; 95% CI = 95% Confidence Interval; NTS = number too small

[a] Adjusted for age, sex, ethnic self-identification, lifetime alcohol use, and lifetime tobacco use.

[b] Conditional on the positive response to the PE, "Caused physical problems."

[c] Conditional on the positive response to the PE, "Caused problems with emotions."

[d] Conditional on the positive response to the PE, "Caused physical problems."

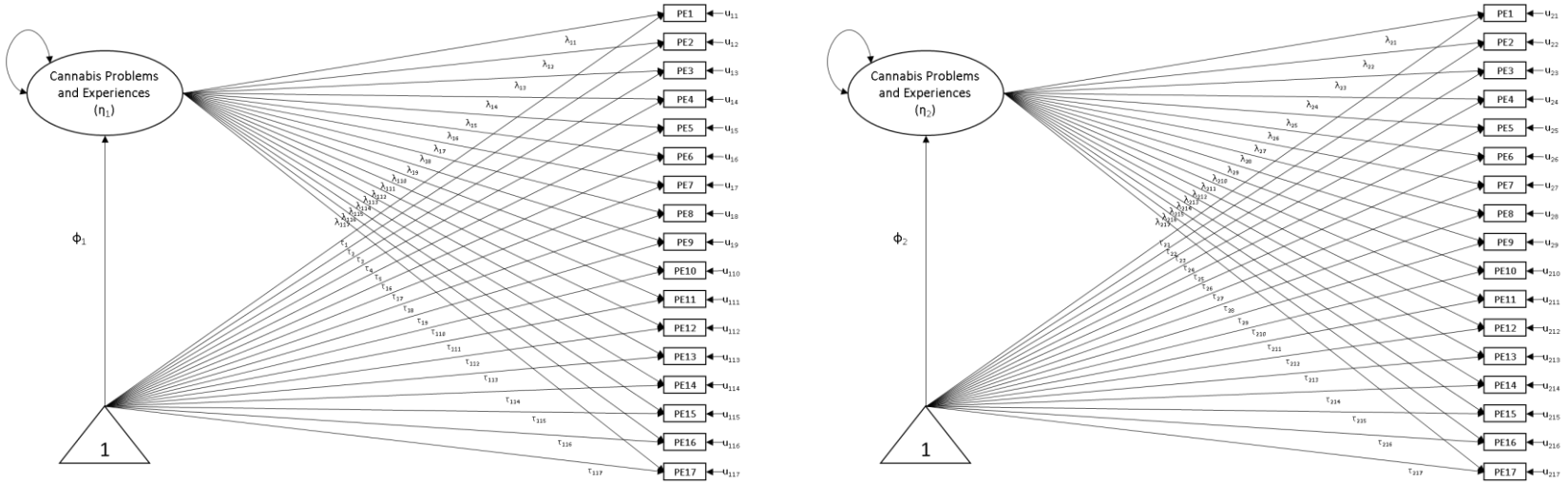
[e] Conditional on the positive response to the PE, "Wanted/Tried to cut down or stop using cannabis."

Table 3.10. Frequency of newly incident cannabis users in each pair of CUD-associated PE within the 12-month interval among polydrug cannabis users (darker shade) and among cannabis only users (lighter shade). * Frequency in each diagonal cell (no shade) is the total number of newly incident cannabis users for individual PE irrespective of IRD status. Data are from the National Survey on Drug Use and Health, 2004-2014 (n=11,838).

	Total	**PE1**	**PE2**	**PE3**	**PE4**	**PE5**	**PE6**	**PE7**	**PE8**	**PE9**	**PE10**	**PE11**	**PE12**	**PE13**	**PE14**	**PE15**	**PE16**	**PE17**
Total		2207	1047	569	448	353	227	303	463	292	145	341	163	126	96	42	131	134
PE1	435	**2642**	607	309	304	251	126	183	329	213	121	259	104	97	74	26	131	107
PE2	431	235	**1478**	343	244	200	149	176	137	172	98	162	104	0	49	21	71	49
PE3	244	129	198	**813**	125	120	84	107	0	97	64	107	75	16	31	11	41	27
PE4	166	103	123	71	**614**	160	227	108	75	140	45	138	83	27	44	10	34	38
PE5	158	95	127	72	77	**511**	84	85	60	156	48	123	76	20	31	8	36	34
PE6	108	60	89	55	108	56	**335**	64	39	73	27	71	62	13	26	7	30	11
PE7	133	82	101	63	57	58	44	**436**	28	68	29	88	55	13	26	9	24	28
PE8	84	45	51	0	22	20	14	16	**547**	54	23	65	27	27	17	7	21	26
PE9	122	80	94	57	67	81	49	47	18	**414**	34	102	55	17	39	8	33	29
PE10	67	59	56	41	31	28	25	23	7	25	**212**	42	26	8	7	7	44	13
PE11	111	75	79	53	55	56	38	39	18	49	24	**452**	163	32	33	4	23	40
PE12	68	41	55	37	37	39	32	31	7	36	17	68	**231**	8	21	0	16	0
PE13	18	10	0	4	5	4	1	3	4	2	1	5	1	**144**	6	2	4	12
PE14	46	30	34	25	30	22	22	22	7	24	11	21	11	4	**142**	1	8	7
PE15	17	7	17	9	5	13	4	6	1	9	3	0	0	0	1	**59**	6	42
PE16	51	51	44	24	20	21	17	17	5	16	30	16	13	0	7	4	**182**	11
PE17	34	22	27	15	11	19	4	13	5	14	4	6	0	1	4	17	6	**168**

*__PE1:__ Wanted/Tried to cut down or stop using cannabis; __PE2:__ Spent a lot of time getting or using cannabis; __PE3:__ Needed more to get the same effect; __PE4:__ Caused problems with family or friends; __PE5:__ Spent less time doing important activities; __PE6:__ Contd. use despite problems w/ family or friends; __PE7:__ Used cannabis and did dangerous activities; __PE8:__ Used the same amount but had less effect; __PE9:__ Caused serious problem at home or work or school; __PE10:__ Was not able to keep limits; __PE11:__ Caused problems with emotions; __PE12:__ Contd. use despite emotional problems; __PE13:__ Spent a lot of time getting over effects; __PE14:__ Caused repeated problems with the law; __PE15:__ Contd. use despite physical problems; __PE16:__ Was not able to cut or stop; __PE17:__ Caused physical problems;

Figure 3.2. Factor model of cannabis problems and experiences and 17 indicators for newly incident cannabis users whose onset occurred (a) within months 1-6 prior to the assessment and (b) within months 7-12 prior to the assessment measurement invariance.* Data are from the National Surveys on Drug Use and Health, 2004-2014 (n=11,838).



(a) Months 1-6 **(b) Months 7-12**

*** PE1:** Wanted/Tried to cut down or stop using cannabis; **PE2:** Spent a lot of time getting or using cannabis; **PE3:** Needed more to get the same effect; **PE4:** Caused problems with family or friends; **PE5:** Spent less time doing important activities; **PE6:** Contd. use despite problems w/ family or friends; **PE7:** Used cannabis and did dangerous activities; **PE8:** Used the same amount but had less effect; **PE9:** Caused serious problem at home or work or school; **PE10:** Was not able to keep limits; **PE11:** Caused problems with emotions; **PE12:** Contd. use despite emotional problems; **PE13:** Spent a lot of time getting over effects; **PE14:** Caused repeated problems with the law; **PE15:** Contd. use despite physical problems; **PE16:** Was not able to cut or stop; **PE17:** Caused physical problems.

Several important secular trends issues worth consideration, including the possibilities that (1) increased levels of psychoactive cannabinoids in currently marketed cannabis might promote a more rapid and increased proportion of users who become dependent as suggested by Compton and others (Compton and Volkow 2006), and (2) changes in the regulatory and social environments for cannabis use might be followed by a more heterogeneous set of newly incident cannabis users, including heterogeneity in relation to host susceptibility. That is, even without exposure to increasing psychoactive cannabinoid contents of products, the mix of susceptibility traits in newly incident users might be shifting toward individuals who are more vulnerable to development of cannabis problems. These possibilities receive some limited empirical support in estimates contributed by the NSDUH research team (e.g., Forman-Hoffman, Glasheen, and Batts 2017), including the suggestion that as many as one in six cannabis users in the age 12-to-14-years-old group has developed a cannabis dependence syndrome within 12 months after starting to use cannabis.

Several of the important limitations are worth noting before detailed discussion. With respect to uncontrolled confounders, our study did not account for susceptibility to cannabis use and dependence due to the lack of susceptibility information (e.g., genetic variants). The absence of adjustment might bias the estimates in favor of positive association as 'cannabis+IRD' users might be more susceptible in developing cannabis-related problems and experiences. Such issue can be addressed in studies such as Adolescent Brain Cognitive Development (ABCD) study, in which genetics and brain functions are rigorously assessed.

With respect to the NSDUH response rates, the screening interview rates and main interview rates show down-ward trend since around 2002, resulting in declining overall NSDUH response rates (from ~72% in 2002 and ~53% in 2016) (United States 2017a; Czajka and Beyler

2016). The high nonresponse rate affects the results if nonresponse is associated with drug use (e.g., greater number of non-respondents among 'cannabis+IRD' users).

With respect to the temporal order, there is no information on the timing of the development of CUD-associated PEs. Based on the information available, there are two possible explanations of the findings, and each possibility has potential public implications. One possibility resonates with gateway process in which cannabis onset is followed by the onset of IRD(s), which is then followed by the onset of CUD-associated PEs. The reported increased risk of cannabis dependence might a result of cannabis-IRD interactions, as cannabis has been reported to have influenced the effect of other drugs in the body system (e.g., Lukas et al. 1994; Freeman and Murphy 2016). Another possibility resonates with the steppingstone process in which cannabis onset is followed by the onset of CUD-associated PEs, which motivates the onset of IRD to relieve the PEs that manifest as symptoms of cannabis dependence. The use of cannabis may lead to physiological need for similar but stronger experiences using other illegal drugs (Pudney 2003). Individual-level interventions might help reduce the risk of developing cannabis dependence, which might prevent the escalation of use from cannabis to other illegal drugs (e.g., Haney et al. 2004; Budney et al. 2007; Haney et al. 2008).

Another important limitation to note is the reliance on self-report measures of drug-related behavior without toxicological biomarkers, although feasible alternatives to self-report in the context of national surveys are very limited. Lastly, children under age 12 are excluded from NSDUH sampling. Drug onsets that occurred before age 12 are not captured in the survey.

Notwithstanding limitations such as these, the study draws strength from its standardized assessment of cannabis experiences and problems in 11 nationally representative samples, external generalizability of the findings, and large annual samples. Its implications might be

important as US policy makers adapt to a changing cannabis regulatory environment and seek to reduce the risk of cannabis dependence among an apparently increasing number of newly incident cannabis users (Johnson et al. 2015; Hasin, Saha, et al. 2015a; Hasin 2017). Another important implication involves intervention at the school level in which school counsellors might provide counselling to students who have used cannabis to reduce the risk of extending drug repertoire to include other IRDs. This study notes that more than 1/2 of the newly incident cannabis users are individuals age 12-17.

This study found evidence of an excess odds of developing CUD-associated PEs among newly incident cannabis users with IRD onset. Our findings are consistent with those published by Lopez-Quintero and Anthony (Lopez-Quintero and Anthony 2015b). These findings have important implications as we seek to reduce the risk of cannabis dependence now that recent findings suggest increasing prevalence of cannabis use in the US (e.g., see Johnson et al. 2015; Hasin et al. 2015). One might suggest to reduce the opportunities of cannabis users to be in contact with users of other IRD by separating cannabis market, similar to that implemented in the Netherlands where cannabis is consumed in "coffee shops" with restriction from using other drugs such as alcohol (MacCoun 2011). This separation of drug markets will address the issue of whether a cannabis dependence process might be slowed or prevented when a newly incident cannabis user avoids taking other internationally regulated drug compounds. Also, future studies on cannabis dependence may investigate different cannabis-IRD combinations and differentiate concurrent users of multiple drugs from simultaneous users as variations within subgroups exist (e.g., alcohol and marijuana used concurrently (Banks et al. 2017) and simultaneously (Lipperman-Kreda et al. 2017). Lastly, in future research that builds on findings such as these, it may be possible to further investigate this relationship with explicit temporal sequence (e.g.,

longitudinal study), although longitudinal studies on drug users face issues related to measurement reactivity that arise from attrition due to loss of participants during follow-up.

CHAPTER 4: POLYDRUG CANNABIS USE AND CANNABIS DEPENDENCE: A LATENT CLASS ANALYSIS (MANUSCRIPT 2)

Abstract

Aim: Roughly 1-in-10 cannabis users in the United States (US) develop cannabis dependence, irrespective of other IRD use. A growing body of evidence suggests that "cannabis only" users have lower risk of drug-related problems (e.g., cannabis dependence syndrome) compared to cannabis users who also use any other internationally regulated drugs (IRD). However, little is known to what extent this estimate is influenced by the use of other IRD. Using a latent class approach, this study aims to identify subgroups of newly incident cannabis users based on the IRD onset within few months after cannabis onset, with investigation on the extent to which memberships in these subgroups might signal an increased risk of developing cannabis dependence, and to investigate variation in latent classes of cannabis users.

Method: With a study population defined to include all non-institutionalized civilian residents of the United States, age 12 years and older, the NSDUH identified 6992 newly incident cannabis users, after multistage sampling and standardized computer assisted interviews. Using latent class analysis, this study identified three latent classes, with one known class consisting of cannabis only users. Odds ratios were then estimated to compare the occurrence of cannabis dependence between the identified latent classes. For the second aim of this study, two half-sample replicates were formed and used to identify latent classes of cannabis users, which were then compared using a multi-group latent class analysis.

Results: Three classes were identified: cannabis only users (class 1); cannabis+analgesics users (class 2); cannabis+hallucinogens users (class 3). Relative to Class Cannabis Only, the cannabis dependence risk ratio estimates are 6.5 (95% CI = 3.9, 11.1) for Class Cannabis+Analgesics and

8.7 (95% CI = 4.5, 17.0) for Class Cannabis+Hallucinogens. Weighted to the US population, the risk ratio estimates are 9.8 (95% CI = 4.5, 21.2) and 9.7 (95% CI = 3.4, 27.5) for these two classes, respectively. Based on the multi-group latent class analysis, there was no difference in the latent structures (L^2 difference test: $\Delta L^2 = 13780.5$, df = 39; p-value>0.999).

Conclusion: Before discussion, methods issues are noted that will confront investigators seeking to improve this work, including self-report measures of drug-related behavior and absence of toxicological assays. The evidence helps strengthen prior findings that cannabis initiates who then use other IRD have increased risk of dependence. The findings reported in this study have important implications in identifying at risk groups for future interventions and treatment strategy. Future studies might investigate other drug-related behaviors (e.g., frequency of use) of the classes identified in this study.

4.1 Introduction

This chapter presents this dissertation's second manuscript, which seeks to identify subgroups of newly incident cannabis users and then to estimate excess occurrence of cannabis dependence for these subgroups. The first section (4.1) states the aims of the research. The second section (4.2) provides a brief background on polydrug cannabis use. The third section (4.3) details the methods used to conduct the investigation. The fourth section (4.4) presents the results of the study. Lastly, the fifth section (4.5) provides a discussion, with coverage of limitations, implications, and conclusions of the study.

4.2 Aim

The main aim of this chapter is to identify cannabis-IRD latent classes among newly incident cannabis users without prior non-cannabis IRD use and to investigate the extent to which membership in these subgroups might signal an increased risk of developing DSM-IV cannabis dependence within an interval of approximately 12 months. To evaluate the identified latent structure, it is compared to another latent structure, which is identified using a replicate sample.

4.3 Background

An increasing body of evidence suggests that cannabis users who use at least one other internationally regulated drug (IRD) have different cannabis-related experiences when compared with 'cannabis only' users (C.-Y. Chen, O'Brien, and Anthony 2005; Lopez-Quintero and Anthony 2015b). This finding opens the following fundamental questions: (1) How much of the risk is attributable solely to cannabis? (2) How much excess risk can be attributed to specific cannabis-IRD combinations? Estimating the unique effect of cannabis by removing the influence of other drugs is a difficult task as it demands more complex study designs (e.g., experimentation) that cannot be conducted without ethical challenges. Therefore, it is not

surprising that efforts to undertake investigations of these issues have been very limited. Although limited by the cross-sectional nature of the present study design, this research addresses these fundamental questions using a latent class approach, which allows identification of subgroups of cannabis users and to compare their risks of developing cannabis dependence. The conceptual model starts with the idea that the risk of cannabis dependence varies across the latent classes of newly incident cannabis users, identified based on the onset of other non-cannabis IRD soon after cannabis onset (Figure 4.1). To investigate whether latent structures of cannabis users in the US population have changed over time, the secondary aim of the study compares the latent structure identified in the first aim to a latent structure from a replicate sample. The replication assembles two independently drawn US population samples.

In the US, epidemiological studies have observed that some cannabis users progress to the use of other internationally regulated drugs (IRD) (Kandel 1975), with excess risk of drug dependence among cannabis users who use other IRD either concurrently or simultaneously (e.g., Lopez-Quintero and Anthony 2015). While an estimated one in 10 cannabis users develop cannabis dependence (J. C. Anthony, Warner, and Kessler 1994), roughly 8% of cannabis users develop cannabis dependence within 10 years after the first time cannabis use (Wagner and Anthony 2002a; C.-Y. Chen, O'Brien, and Anthony 2005; Lopez-Quintero et al. 2011; Wagner and Anthony 2007). In light of the recent liberalization of cannabis use in some states in the US, the prevalence of cannabis use seems to have increased. The use of other non-cannabis drugs, however, seems to have decreased over time (United States 2015). Although more evidence is needed (MacCoun 2011), it can be speculated that separation of the cannabis market might have to do with the reduction of the risk to use other non-cannabis drugs for which risk of toxicity seems to be greater.

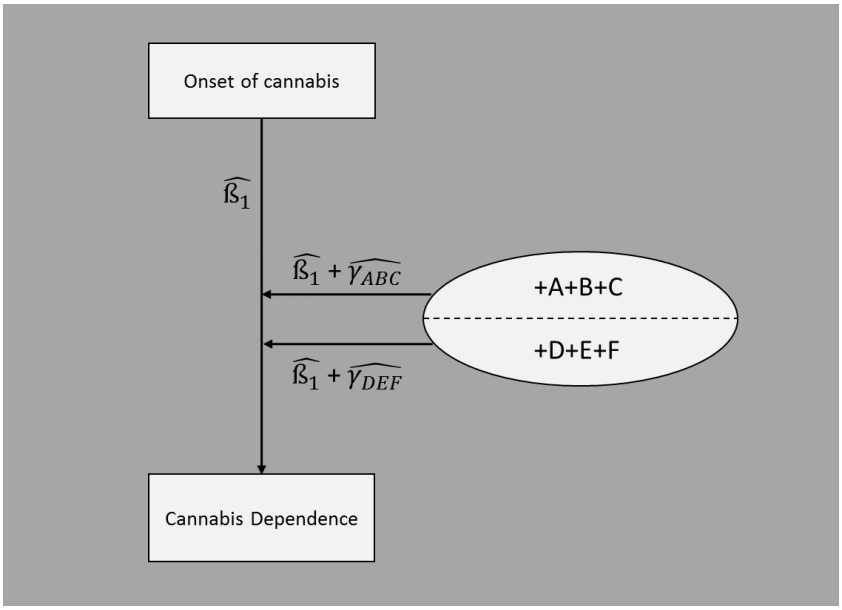
4.4 Methods

4.4.1 Study Population, Sample and Design

The methodological details of NSDUH have been provided in Section 3.3. Briefly, the study population consists of US residents age 12 and older, who are sampled each year for the National Surveys on Drug Use and Health (NSDUH), 2009-2014. To identify the latent structure of polydrug cannabis users, NSDUH years 2012, 2013, 2014 are used. This latent structure is evaluated by comparing it to a latent structure identified using NSDUH years 2009, 2010, 2011. Readers knowledgeable about NSDUH may wonder about data from more recent years. NSDUH reports suggest that it is difficult to compare all IRD estimates from years before 2015 with estimates from 2015 forward due to major methods changes, especially with respect to prescription drugs. For this reason, this study's samples extend only to 2014.

For this annual cross-sectional survey, contract staff working for the Substance Abuse and Mental Health Service Administration (SAMHSA) employ multi-stage sampling to draw, recruit and assess nationally representative community survey samples of non-institutionalized civilian residents age 12 years and older prior to recruitment and assessment with informed assent/consent. The annual sample, which consists of approximately 70,000 participants, completes a multi-module audio-enhanced computer-assisted self-interview (ACASI) on drug-related behaviors and health topics, after review and approval by cognizant institutional review boards for the protection of human subjects in research (United States, 2015).

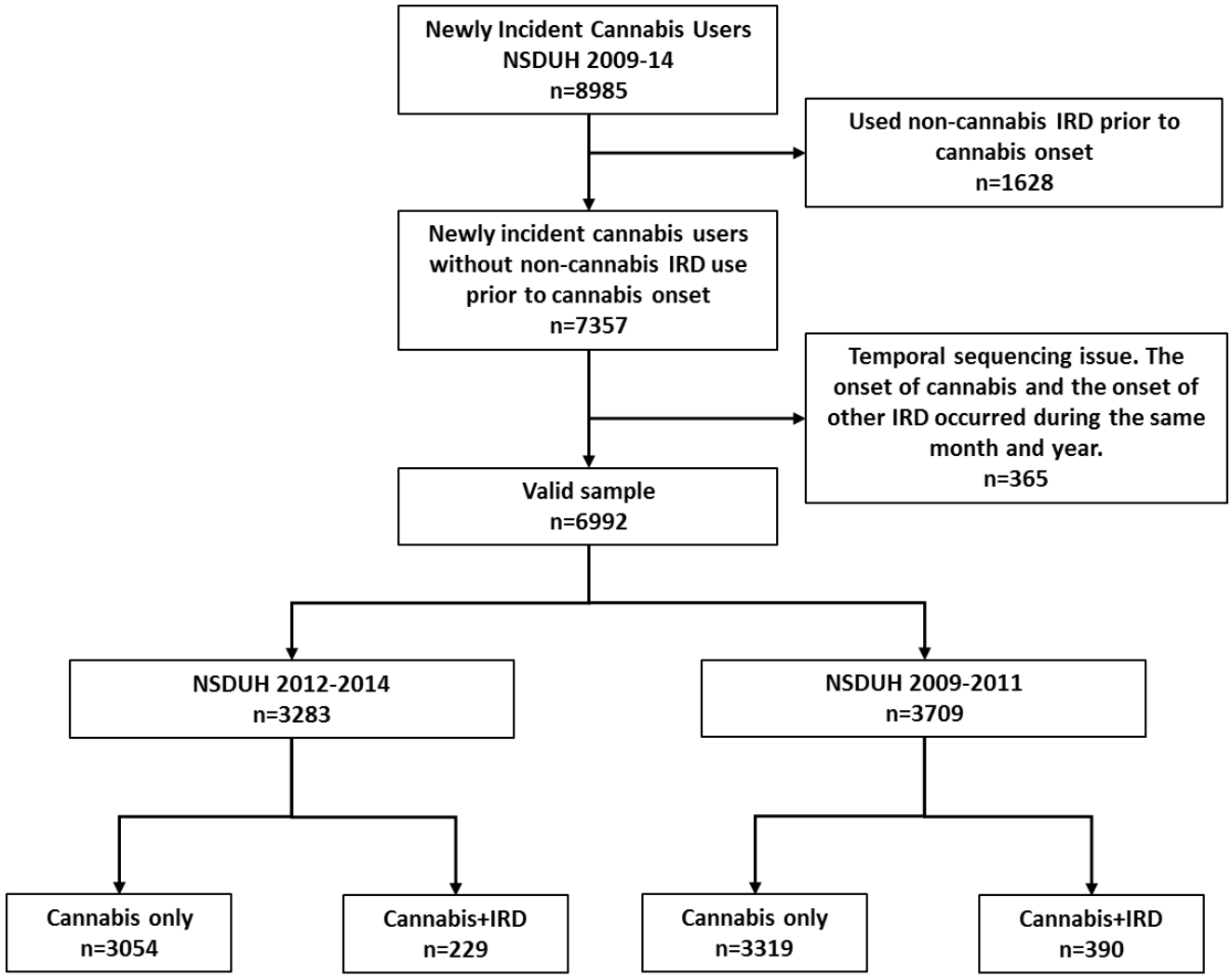
Figure 4.1. The conceptual model depicting the hypothesized association between the cannabis dependence and polydrug use latent classes among newly incident cannabis users.* Data are from the United States National Surveys on Drug Use and Health, 2009-2014.



*An a priori specification of a known class (Class Cannabis Only) was made prior to identification of two other classes. Class Cannabis Only served as the reference when potential variation of cannabis dependence risk estimates across classes was investigated.

This study sample consists of newly incident cannabis users who have never used any other IRD prior to cannabis onset. Figure 4.2 shows a flowchart of selection based on pre-specified criteria. Combined across the six NSDUH survey years, 8985 newly incident cannabis users were identified, of whom 1628 have started using other IRD prior to the cannabis onset. The remaining sample of 7357 includes 365 individuals who have started using other IRD during the same month and year of cannabis onset. Due to the uncertainty of the order of the drug onset, these 365 individuals were excluded. The resulting valid sample is 6992 (n=3709 for NSDUH 2009-11; n=3283 for NSDUH 2012-14). For the primary aim of this study, the latent class analysis was conducted using the combined NSDUH years 2012-2014 (Figure 4.2). For the second aim, the multigroup latent class analysis was conducted to compare two latent structures, each from the two sets of combined NSDUH data (NSDUH 2009-2011 and NSDUH 2012-2014).

Figure 4.2. Flow chart identifying newly incident cannabis users whose IRD use occurred after cannabis onset. Data from the US National Survey on Drug Use and Health, 2009-2014 (n=6992).



4.4.2 Assessment of the Key Response Variable

The key response variable is the onset of cannabis dependence (DSM-IV) soon after cannabis onset but always within 12 months prior to the NSDUH assessment. For each survey year, problems and experiences related to cannabis use are assessed among individuals who have used cannabis at least one day within the past 12 months prior to the assessment. Several of these problems and experiences refer to clinical features of DSM-IV cannabis dependence (American Psychiatric Association and American Psychiatric Association 2000)), which are below:

1. Spent a great deal of time over a period of a month getting, using, or getting over the effects of marijuana;
2. Used marijuana more often than intended or was unable to keep set limits on use;
3. Needed to use marijuana more than before to get desired effects or noticed that same amount of marijuana use had less effect than before;
4. Inability to cut down or stop using marijuana every time tried or wanted to;
5. Continued to use marijuana even though it was causing problems with emotions, nerves, mental health, or physical problems;
6. Marijuana use reduced or eliminated involvement or participation in important activities.

As shown in Table 2.1, diagnosis of DSM-IV cannabis dependence requires meeting at least three of the six clinical features.

4.4.3 Measurement of the Covariate of Central Interest

The covariate of central interest is the onset of cannabis use and extra-medical use of at least one non-cannabis IRD, both occurred within the 12-month interval, measured via self-reported month and year information of IRD onset. NSDUH participants respond to drug-use module of

the assessment, in which participants are asked about the timing of their drug onset. Standardized questions on cannabis and other IRD use questions were as follows, irrespective of medical or extra-medical use:

- Have you ever, even once, used [IRD]?
- How old were you the first time you used [IRD]?
- Did you first use [IRD] in [CURRENT YEAR-1], or [CURRENT YEAR]?
- In what month in [YEAR] did you first use [IRD]?

Responses to these questions were used in order to determine valid cases, who are newly incident cannabis users without any prior IRD use. These cases include 'cannabis only' users, who have not started use of any of the other IRD, and those with post-cannabis onset of one or more of the following: cocaine, crack cocaine, methamphetamine, other 'stimulants,' heroin, OxyContin, other 'prescription pain relievers' (generally opioids)**, '**inhalants,' 'sedative-hypnotics,' 'PCP,' 'hallucinogens,' 'LSD,' 'ecstasy,' and 'tranquilizers' (i.e., anxiolytic products).

4.4.4 Conceptual Model

The conceptual model of this study begins with the idea that the risk of cannabis dependence varies across latent classes of newly incident cannabis users, identified based on the onset of other non-cannabis IRD after cannabis onset within approximately 12 months prior to the NSDUH assessment (Figure 4.1). Latent classes of polydrug cannabis use are identified using binary indicator variables on responses to the items the timing of the onset of 13 drugs soon after cannabis use. The latent class analysis characterizes the relationships and the patterns of co-occurrence of these observed binary indicators.

4.4.5 Statistical Analyses

4.4.5.1 Latent Class Analysis

In brief, finite mixture models such as latent class models address issues that require identification and characterization of subgroups underlying within a population. Mixture models assume that an observed sample of a study population might be composed of a mixture of two or more classes of population members, with class membership based on responses to multiple observed items. The overall distribution of these observed items are expressed as a mixture of finite number of less complex component distributions obtained from individual items (Masyn 2013). One way to identify these subgroups is by using latent class analysis to create mutually exclusive classes, each of which is comprised of individuals with similar responses to the observed variables.

The probability of observing an individual (***i***) with a specific response pattern (***v***) is a function of two components: 1) the probability of observing the individual being in one of the classes (**L**); and 2) the probability of the individual to have the response pattern given that the individual has membership in the latent class. The probability of observing the specific response pattern can then be simply expressed as follows:

$$Pr\{Y_i = v\} = \sum_{l=1}^{L} P(L = l)\, P(Y_i = v \,|L = l). \qquad \text{(EQ. 4.1)}$$

The expression $P(Y_i = v \,|L = l)$ can be further expressed as:

$$P(Y_i = v \,|L = l) = \prod_{m=1}^{M} \prod_{c_m}^{C_m} \rho_{m,c_m|l}^{I(v_m = c_m)}, \qquad \text{(EQ. 4.2)}$$

for data with m=1,…,M measured observed variables, and the observed variable m has c_m = 1,…, C_m categorical responses (i.e., $C_m = 2$). $I(v_m = c_m)$ is a function that indicates whether ρ is to be multiplied (value is 1 when $m=c_m$) or not (value is 0 if $m \neq c_m$).

There are two major approaches in conducting latent class analysis: (1) one-step approach where the relationship between latent class membership and outcome variable are estimated simultaneously; and (2) three-step approach where the relationship between latent class membership and outcome variable are estimated in a step-wise process. One-step approach is preferable statistically when basic model assumption holds. The three-step approach is preferable when the interest is the predictive validity of the indicators. For this reason, this study uses the three-step approach to predict the onset of cannabis dependence using IRD-onset latent class indicators. One concern, however, is that three-step approach yields downward-biased estimates of the model parameters that measure the relationship between class membership and outcome variable (Bolck, Croon, and Hagenaars 2004; Vermunt 2010). Statistical adjustments have been proposed (Vermunt 2010; Bakk, Tekle, and Vermunt 2013) and have been employed in the statistical software Latent GOLD® 5.1 (Statistical Inovations Inc. 2016). All analyses in this study were conducted using this version of Latent GOLD.

4.4.5.2 Analysis Plan

The statistical analysis began with estimation of year-by-year transition probabilities of developing DSM-IV cannabis dependence between 'cannabis only' users and 'cannabis+IRD' users. Taylor series linearization was used to estimate the variances of the probability estimates to account for the multi-stage sampling design. The probability estimates and their variance estimates were then summarized using meta-analytic approach, via 'random effects' estimator.

The latent class modeling approach employed in this study are exploratory in nature. For the first aim of this study, a three-step approach in performing latent class analysis was used: (1) identify the number of latent classes; (2) assign individuals to their respective latent classes; and (3) estimate the odds of cannabis dependence on latent class membership indicators. To

determine the number of latent classes, an exploratory class enumeration step approach suggested by Masyn (2013) was conducted. Observations were randomly allocated into classes, and *k*-number of latent class models were fitted, where *k* is the maximum number of classes to obtain an identifiable model. Evaluation of model fit is based on Likelihood Ratio Chi-square (X^2_{LR}), Bayesian Information Criterion (BIC), Consistent Akaike Information Criterion (CAIC), Approximate Weight of Evidence Criterion (AWE), Bootstrapped Likelihood-Ratio Test (BLRT), and relative entropy. After obtaining the number of latent classes with a "best" fitting model, each observation was assigned to latent classes using their posterior class membership probabilities. Then, the odds of developing cannabis dependence was regressed on class membership indicators using logistic regression with a pre-specified 'Cannabis Only' class as the reference class.

For the second aim of this study, the resulting model from the first aim using NSDUH 2012-2014 (see Figure 4.2) was compared to another model obtained using an independently drawn population sample (NSDUH 2009-2011; see Figure 4.2). A multi-group latent class approach was used by fitting a heterogeneous model (without any parameter constraint) and a homogeneous model (with parameter constraints) (Magidson and Vermunt 2004), and each model's likelihood ratio chi-squared statistics (L^2) was then compared. Fitting a heterogeneous multi-group latent class model is equivalent to fitting latent class model for each group separately. In this research, this model can be expressed by modifying EQ. 1 as below:

$$Pr\{Y_i = v|G = g\} = \sum_{l=1}^{L} P(L = l|G = g)\, P(Y_i = v\,|L = l, G = g). \qquad \text{(EQ. 4.3)}$$

where *G* is the group variable with 1,…, g groups. Fitting a homogenous multi-group latent class model is conducted by constraining either the item response probabilities or the size of the latent

classes or both. In this study, a homogeneous model with equality constraint on the item response probabilities of both groups was conducted. Such model can be expressed as follows:

$$Pr\{Y_i = v|G = g\} = \sum_{l=1}^{L} P(L = l|G = g)\, P(Y_i = v\,|L = l). \qquad \text{(EQ. 4.4)}$$

The two models were then compared using a difference test based on the difference of each model's L^2 values (Magidson and Vermunt 2004).

4.5 Results

4.5.1 Results for Primary Aim

Table 4.1 describes the study sample and presents the risk estimates of cannabis use subgroup aggregated across three survey years: 2012, 2013, 2014. The year-specific sample descriptions and estimates are presented in Appendix B, which also shows the meta-analysis forest plot of the three year-specific estimates, along with the 1.9% estimate presented in Table 4.1 and its 95% confidence interval based on the Laird-DerSimomian random effects estimator. Table 4.1 shows the initial meta-analytic analysis-weighted estimates from logistic regression for the risk of developing cannabis dependence soon after new cannabis use (i.e., prior to latent class membership is considered). As shown in the first two rows of estimates, an estimated 1.9% of the 'cannabis only' stratum had developed a cannabis dependence syndrome between the month of first cannabis use and the date of survey assessment, no more than one year since first cannabis use. None of the new cannabis users in this stratum had started to use other IRD under study.

Students of public health may appreciate that this 1.9% estimate has some resemblance to an 'attack rate' as defined for post-exposure investigations of outbreaks of food-borne illnesses, with a numerator consisting of observed cases by the time of post-exposure assessment, and with a denominator consisting of the number of exposed persons (Lopez-Quintero & Anthony, 2015).

Table 4.1. Sample Description and Weighted Risk Estimates of Cannabis Dependence. Data are from the US National Surveys on Drug Use and Health, 2012-2014 (n= 3283 newly incident cannabis users).

		DSM-IV Cannabis Dependence				
		Meta-analytic summary estimate				
	Total	Unweighted			Weighted	
	n	n	%	95% CI	%	95% CI
Cannabis only	3054	67	2.2	1.7, 2.8	1.9	1.2, 2.9
Cannabis+IRD	229	32	14.0	10.0, 19.1	15.7	8.1, 30.4

Table 4.2. Goodness-of-Fit Indices Comparing Class Models of Polydrug Cannabis Use Among Newly Incident Cannabis Users. Data are from the National Surveys on Drug Use and Health, 2012-2014 (n=3283).

Model	# of classes*	# of par	LL	X^2_{LR}	df	p-value	BIC	CAIC	AWE	BLRT	Entropy
1	2	13	-918.7	3653003.2	216	<0.001	1908.0	1921.0	2017.6	<0.001	1.00
2	3	27	-818.9	89344.0	202	<0.001	1784.5	1811.5	2026.1	<0.001	0.99
3	4	41	-789.4	91586.8	188	<0.001	1801.6	1842.6	2165.4	<0.001	0.98
4	5	55	-767.4	90328.1	174	<0.001	1833.7	1888.7	2319.5	<0.001	0.98
5	6	69	-747.6	19613.9	160	<0.001	1870.0	1939.0	1939.0	<0.001	0.97
6	7	83	-733.5	39328.7	146	<0.001	1918.0	2001.0	2652.6	<0.001	0.97
7	8	97	-720.5	39395.9	132	<0.001	1968.0	2065.0	2818.8	0.002	0.97
8	9	111	-709.4	1141.9	118	<0.001	2021.9	2132.9	2975.7	<0.001	0.98

* The value under this column is the number of latent class including 'cannabis only' class (known class), which was excluded in the enumeration step.

Person-months of follow-up are not considered, given the relatively short interval of time passing between the month of first cannabis use and the assessment.

Table 4.2 presents goodness-of-fit indices comparing the fitted k-number of latent class models. Eight of the fitted latent class models are shown because indices suggest no improvement in model fit for models with a greater number latent classes, indicated by the increasing BIC, CAIC and AWE values. Based on the BIC and CAIC, Model 2 has the smallest values for both criteria (1784.5 and 1811.5, respectively); therefore, the model was chosen for the next steps in the analysis plan.

The item-response probabilities for Model 2 are presented in Figure 4.3. The pre-specified Class 1 (Class Cannabis Only) is comprised of cannabis only users, as indicated by what I specified as a zero response probability for each non-cannabis IRD. Members of Class 2 labeled as Class Cannabis+Analgesics exhibited a high probability of pain-reliever onset and relatively high probabilities of other stimulants onset, anxiolytics onset and inhalants onset. Members of Class 3 labeled as Class Cannabis+Hallucinogens demonstrated a high onset probability of hallucinogens and relatively high probabilities of Ecstasy onset, LSD onset, and analgesics onset.

4.5.2 Group Comparison

Table 4.3 presents the item-response probabilities conditional on the latent class membership for each comparison group. For visual comparison, the plot of these item-response probabilities is presented in Figures 4.3 and 4.4 for combined NSDUH years 2012-2014 and combined NSDUH years 2009-2011 respectively. As described in the Methods section, the "Cannabis Only" class was pre-specified to have zero probabilities with respect to non-cannabis IRD. The pooled analyses from 2012-2014 data elicited two other classes, which I labeled based on the probability

Table 4.3. Item response probabilities of newly incident cannabis users conditional on latent class membership. Data from the National Surveys on Drug Use and Health, United States, 2009-2014 (n=6992 newly incident cannabis users).

	NSDUH 2012-2014			**NSDUH 2009-2011**		
Recent onset Item	Cannabis Only	Cannabis + Analgesics	Cannabis+ Hallucinogens	Cannabis Only	Cannabis + Analgesics	Cannabis+ Hallucinogens
Cocaine	-	0.062	0.044	-	0.080	0.068
Methamphetamine	-	0.000	0.005	-	0.001	0.013
Other Stimulants	-	0.152	0.112	-	0.147	0.101
Heroin	-	0.000	0.005	-	0.008	0.000
Analgesics	-	0.556	0.214	-	0.531	0.240
OxyContin	-	0.060	0.090	-	0.071	0.075
PCP	-	0.000	0.024	-	0.000	0.028
Ecstasy	-	0.000	0.451	-	0.000	0.601
Hallucinogens	-	0.000	1.000	-	0.058	1.000
LSD	-	0.000	0.196	-	0.000	0.176
Anxiolytics	-	0.173	0.108	-	0.163	0.144
Inhalants	-	0.190	0.025	-	0.275	0.142
Sedatives	-	0.040	0.038	-	0.045	0.042

Figure 4.3. Item-Response Probabilities Conditional on Latent Class Membership. Data are National Surveys on Drug Use and Health, 2012-2014 (n=3283 newly incident cannabis users).

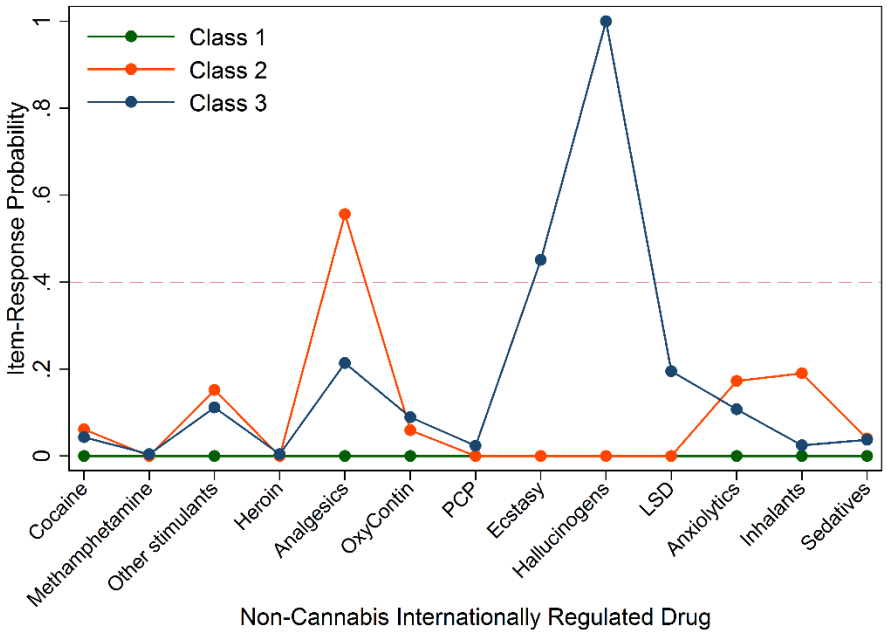


Figure 4.4. Item-Response Probabilities Conditional on Latent Class Membership. Data are National Surveys on Drug Use and Health, 2009-2011 (n=3709 newly incident cannabis users).

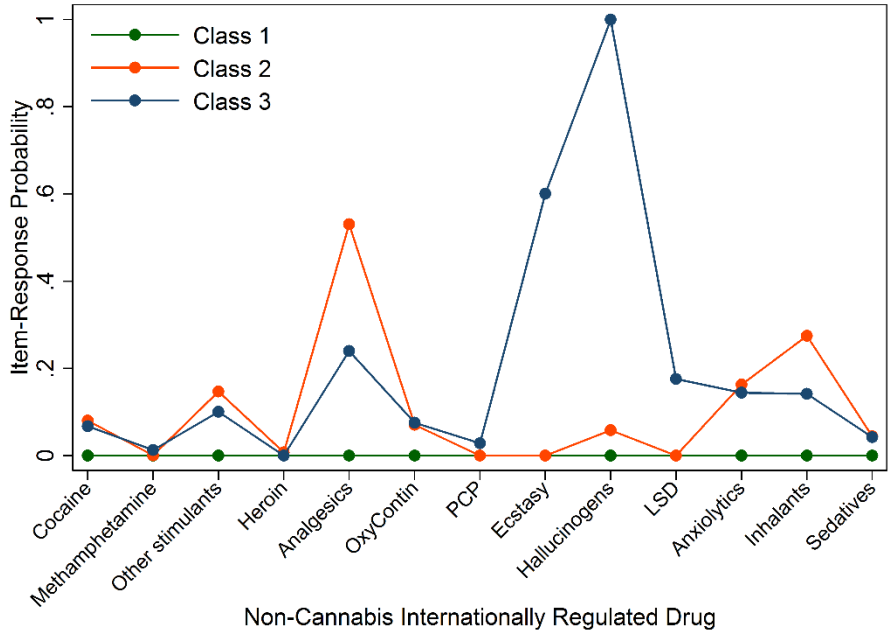


Table 4.4. Goodness-of-Fit Indices Comparing the Restricted and Unrestricted Multilevel Latent Class Models of Polydrug Cannabis Use Among Newly Incident Cannabis Users. Data are from the National Surveys on Drug Use and Health, 2009-2014 (n=3283).

Model	**Description**	**# of par***	**BIC_{LL}**	**L^2**	**DF**	**L^2 p-value**	**ΔL^2**
$M_{unrestricted}$	3-class unrestricted (heterogeneous)	82	1186267.8	214041.8	16300	<0.001	0
$M_{restricted}$	3-class restricted (homogeneous)	43	1199580.1	227822.3	16339	<0.001	13,780.5
L^2 Difference Test: $\Delta L^2 = 13780.5$, df = 39						p-value >0.999	

*number of parameters

estimates shown in Figure 4.3. The label for one class of these new cannabis users is "Cannabis+Analgesics," in that analgesics seem to be the only other IRD sub-type with at least 40% using extra-medically. (The dotted line in Figure 4.3 is at the 40% level as an aid to visualization.)

The label for the other class is "Cannabis+Hallucinogens" and is based on a similar standard. Please note that Ecstasy is a street name for 3,4-methylenedioxymethamphetamine, which often is grouped as a 'hallucinogen or mixed stimulant-hallucinogen, so I did not use the label "Cannabis+Hallucinogens+Ecstasy." I also should note that LSD also is grouped as one of the Hallucinogens, but it was used by only about 20% of new cannabis users, well below my chosen standard of 40%. Figure 4.4 presents the corresponding plot based upon data from pooled analyses of 2009-2011 data. From visual inspection, it would seem that the labels from 2012-2014 also apply here.

Table 4.4 presents the goodness-of-fit indices for unrestricted multi-group latent class model and the restricted multi-group latent class model. Based on the $BIC_{LL'}$ Model $M_{unrestritced}$ would be a favorable model, with lower value compared to Model $M_{restricted}$ (1186267.8 vs. 1199580.1). To evaluate the difference, I used a likelihood ratio chi-squared statistic L^2. There

Table 4.5. Weighted Odds Ratio Estimates of DSM-IV Cannabis Dependence Among the Three Latent Classes. Data are National Surveys on Drug Use and Health, 2009-2014 (n=6992 newly incident cannabis users).

	NSDUH 2009-2011		NSDUH 2012-2014	
Class			**OR**	**95% CI**
Cannabis Only	-	-	-	-
Cannabis + Analgesics	3.1	1.7, 5.7	9.8	4.5, 21.2
Cannabis + Hallucinogens	7.0	2.8, 17.5	9.7	3.4, 24.5

was an increase in L^2 value from 214041.8 to 227822.3 from unrestricted to when the item-response probabilities were constrained. However, the ΔL^2 difference test suggests no statistically significant difference between the two models. This also means that there is no evidence that the latent structures in NSDUH 2009-2011 are different from the latent structures in NSDUH 2012-2014. This analysis helps confirm the fundamental congruence apparent in visual comparison of Figures 4.4 and 4.5.

Class-specific estimates of the odds of cannabis dependence are compared (Table 4.5). When compared to Class Cannabis Only, Class Cannabis+Analgesics have greater odds of developing cannabis dependence (NSDUH 2009-2011: OR=3.1; 95% CI = 1.7, 5.7; NSDUH 2012-2014: OR = 9.8; 95% CI = 4.5, 21.2). Similar results are found Class Cannabis+Hallucinogens (NSDUH 2009-2011: OR = 7.0; 95% CI = 2.8, 17.5; NSDUH 2012-2014: OR = 9.7; 95% CI = 3.7, 24.5).

4.6 Discussion and Conclusion

The main findings of this study can be summarized succinctly. First, three latent classes of newly incident cannabis users were identified after pre-specification of a class with members who were 'cannabis only' users (Class Cannabis Only); (1) an analgesics class, identified by high response probability to analgesics onset (Class Cannabis+Analgesics); and (2) a hallucinogens class,

marked by high response probability to hallucinogens onset (Class Cannabis+Hallucinogens). Second, when compared to Class Cannabis Only, members of Class Cannabis+Analgesics and Class Cannabis+Hallucinogens have greater risks of developing cannabis dependence. Third, the latent structures did not differ appreciably across the survey years under study.

This study's findings of excess risk of cannabis dependence among cannabis users who used other non-cannabis IRD when compared to cannabis only users are consistent to prior studies (von Sydow et al. 2002; Lopez-Quintero and Anthony 2015b; Hines et al. 2016). Prior studies on polydrug use involving classes of cannabis users are not comparable to this study because it is the first to have investigated newly incident cannabis users. The prior studies combined large numbers of past-onset users together with small numbers of newly incident users, did not exclude past-onset IRD users, and did not investigate rapid transitions from cannabis use to other IRD use (e.g., Wu et al. 2009; Krauss et al. 2017).

Before detailed discussion of the findings, several limitations are worth noting. Of central concern is the potential left-truncation due to outcomes related to drug use. For example, newly incident cannabis users might start using heroin and cocaine simultaneously (a combination known as 'speedball') and experience a fatal overdose. This would seem to be a remote possibility, but it can occur(Rivera et al. 2018). Another limitation is the reliance on self-report survey assessment on drug dependence and the timing of drug onset. Alternatives to self-report assessment include toxicological assays, which measure drug use more accurately but these assays are infeasible for large sample nationally representative sample surveys, with rare exceptions (United States 2014). With respect to the NSDUH participation levels, a declining since 2002 has been reported (United States 2017a; Czajka and Beyler 2016), affecting the results if nonresponse is associated with drug use. With respect to the study design, the study is

limited by general issues surrounding surveys that are cross-sectional in nature. Lastly, with respect to the temporal sequencing, there is no information on the timing of the development of DSM-IV cannabis dependence, which might precede rather than follow onset of non-cannabis IRD use, once new cannabis use starts. This last issue might prove to be the most serious of these study limitations, and it has prompted a new investigation of how often cannabis dependence emerges within 90-180 days after new cannabis use. A new report on that investigation will be ready for journal submission within a few months.

Despite these limitations, this study provides additional evidence that cannabis users with other non-cannabis IRD use are much more likely to be observed with cannabis dependence, even when the assessment is completed within 12 months after first cannabis use. Fine grained temporal sequencing data on the symptoms of cannabis dependence will be needed to clarify whether CD surfaces quickly and is followed by onset of other IRD use, or the reverse. Causal inference will be difficult until this unresolved issue can be clarified. And even so, it is possible that cannabis initiates who seek other IRD have special susceptibility traits, possibly of genetic origin, that account for these concurrent states being observed after cannabis onsets. The latent class with distal outcome approach allows us to identify distinctive groups of cannabis users and compare their risks on developing cannabis dependence. This approach has an advantage in providing easily interpretable results for public health reporting purposes (i.e., reporting odds ratios) as opposed to the traditional latent class when conducting latent class analysis with a response variable. The findings reported in this study may have important implications and early intervention programs and policies relating to onset of cannabis and other IRD. On this basis, cannabis use policy guided by empirical findings might be in placed to intervene against easy

access to opioids and/or hallucinogens. Another implication relates to providing specialized treatment for cannabis users who also use opioids or drugs with hallucinogenic effects.

One might suggest to reduce the opportunities of cannabis users to be in contact with users of other IRD by separating cannabis market, similar to that implemented in the Netherlands where cannabis is consumed in “coffee shops” with restriction from using other drugs such as alcohol (MacCoun 2011). This separation of drug markets will address the issue of whether a cannabis dependence process might be slowed or prevented when a newly incident cannabis user avoids taking other internationally regulated drug compounds.

CHAPTER 5: NATURAL HISTORY AND CLINICAL COURSE OF THE CANNABIS USE DISORDER: CLUSTERING OF CANNABIS-RELATED PROBLEMS AND EXPERIENCES WITHIN AN INDIVIDUAL (MANUSCRIPT 3)

Abstract

Aims. By definition, cannabis dependence includes the clustering of cannabis-related problems and experiences (PEs) likely indicates occurrence of cannabis use disorder (CUD). In the United States (US), the natural history and clinical course of cannabis use disorder has been studied infrequently. Studying the natural history and clinical course of CUD, this study investigates the occurrence of individual cannabis-related PEs and their covariation during intervals of elapsed time since cannabis onset.

Methods. The study population consists of non-institutionalized US residents age 12 and older, as sampled for the National Surveys on Drug Use and Health (NSDUH), 2004-2014, though multi-stage sampling approach. These 11 nationally representative samples were assessed on drug-related behaviors through computerized self-interview identification after informed assent/consent. The basic details about the study design, sampling, recruitment, assessment, and identification of newly incident cannabis users are provided in the prior chapters.

Cannabis users whose age of onset occurred during the age or prior to the age at assessment state the month and/or year of the cannabis onset. Based on these information, 15896 individuals were identified as newly incident cannabis users who initiated cannabis use within ~15 months prior to the assessment. Of those, 14457 have complete month and year information that is necessary to estimate the elapsed time from onset to assessment. For each of their intervals, pairwise within-subject correlations of 17 CUD-related problems and experiences were estimated, resulting in 136 pairwise correlation estimates and their variance estimates (obtained

using a bootstraping approach). These pairwise combinations were then treated as individual observations, each with 13 “time-point measurements.” Linear mixed regression analysis was used to assess the variation of the estimates over 13 lag-times.

Results. Ranked in order, the two most occurring CUD-related PEs are “want to try to cut down or stop using cannabis” and “spent more time getting or using cannabis.” We can see early within-subject correlation of these two PEs looking across the 136 PE pairs. When looking at all the pairs in each lag-time, visual examination of scatter plots suggests increased correlation estimates for lag-times 2-13 relative to lag-time 1. This observation as captured by the linear mixed model, which results suggest that the mean within-subject pairwise correlation estimate is greater for lag-times 2-13 relative lag-time 1 ($p<0.001$, slopes ranging from 0.051 to 0.230).

Conclusion. This study provides evidence of an increased within-subject pairwise correlation of CUD-related PE, suggesting increased clustering of PE as a dependence syndrome forms. Studying this clustering of CUD-related PE helps us over the course of cannabis involvement allows us to understand the national course cannabis use disorder that will be useful for prevention strategies and interventions.

5.1 Introduction

This chapter presents this dissertation's third manuscript, which concerns the natural history and clinical course of cannabis dependence using stratification by elapsed time since cannabis onset. The first section (5.1) states the aims of the research. The second section (5.2) provides a brief background on cannabis use disorders (CUD) and CUD-related problems and experiences. The third section (5.3) describes the methods used to conduct the investigation. The fourth section (5.4) presents the results of the study. Lastly, the fifth section (5.5) provides a discussion, with coverage of the limitations, implications, and conclusions of the study.

5.2 Aim

The aim of this study is to investigate the covariation of CUD-related problems and experiences among newly incident cannabis users over durations of cannabis use, in which duration is defined as the elapsed time from the month of cannabis onset to the quarter of survey assessment within a 12-month interval. It is expected that elapsed time of cannabis use is associated with increased covariation of CUD-related problems and experiences.

5.3 Background

The occurrence of cannabis use disorder (CUD; e.g., cannabis dependence) in cannabis use research is most often indicated by the clustering of interrelated cannabis-associated symptoms. In the case of cannabis dependence, these manifestations are sometimes broadly categorized as (1) disturbances of mental health, (2) disturbances of behavior, and (3) manifestations of neuroadaptation after cannabis use, which are central in modern case definitions for the cannabis dependence syndrome, with maladaptive use sometimes covered in diagnostic criteria for the cannabis dependence diagnosis (Reed, Storr, and Anthony 2006; J. C. Anthony 2006). Irrespective of the type of symptoms, diagnostic criteria such as those in Diagnostic and

Statistical Manual (DSM) editions simplify the identification of the underlying disorder by specifying a threshold for the number of symptoms for diagnosis (e.g., 3+ symptoms for DSM-IV cannabis dependence and 2+ DSM-5 addiction.) (American Psychiatric Association and American Psychiatric Association 2000; American Psychiatric Association 2013). While concerns about these thresholds have been raised (e.g., Bailey et al. 2000; Hasin et al. 2013), these diagnostic criteria have become used in studies of CUD. By these definitions, there is an explicit requirement for the clustering of symptoms within specified interval of time often declared in intervals of 12 months duration.

Prior studies have investigated the time course of the emergence of cannabis experiences and problems in diagnosed cases of cannabis use disorders. In a diagnosed case, these experiences and problems can be conceptualized as 'symptoms' of an underlying pathological process. However, supposed a newly incident user has just one of such experience that does not qualify the user as a CUD case. This experience does not meet the definition of a symptom or sign as an observable manifestation of an underlying pathological process. It might be merely an experience such as having to spend some time finding a second 'joint' to smoke after being a few puffs on a friend's pipe. There is no pathological process unless and until multiple different kinds of such experiences start to co-vary within the individual. For this reason, in research on the natural history or course of cannabis involvement, it becomes important to study emergence of experiences as they co-vary. Studying these experiences (sometimes symptoms) one by one is not wholly satisfactory. Study of experiences one by one does not reveal the process of a cannabis user undergoes from first time use to a full development of CUD during the insidious CUD onset (Costello 1992, Rosenberg and Anthony 2001).

With knowledge of co-varying experiences emerging at early stages of insidious CUD onset, clinicians may be able to determine the stage of the disorder and provide appropriate treatment. Second, to the extent that clinicians recognize some pairs of experiences, or clusters of experiences as facets of the 'prodrome' of an incipient CUD, an early intervention might help reduce the incidence of CUD. Third, covariation evidence should promote differentiation of the experience of groups of cannabis users with cannabis dependence and those who have not developed dependence. In this study, the experiences are investigated individually and in combination as they emerge rapidly month-by-month from the month at onset to the timing of survey assessment.

To understand the natural history and clinical course of CUD, evidence is needed on the progression from first time cannabis use to possibly more frequent use and CUD within a specific time interval (Wittchen et al. 2008). Although a few studies suggest some symptoms may occur within few days after use (Bass and Martin 2000; Hesse and Thylstrup 2013; Dierker et al. 2017), there now is no clear evidence on the duration of the development of CUD, which might explain the wide variation in the length of the time intervals specified in previously published studies on CUD. The intervals vary widely from daily to almost a decade (Vsevolozhskaya and Anthony 2015; van der Pol et al. 2013b; Farmer et al. 2015). Despite such variation, very few studies have looked at the progression of cannabis experiences month-to-month. Here, the duration of cannabis use was specified to approximately 1-month cannabis use intervals for a description of the course of CUD by estimating its manifestations month-by-month using 11 independent nationally representative samples of US residents.

5.4 Methods

5.4.1 Study Population and Design

The methodological details of US NSDUH have been provided in Section 3.3. For this study, the study population consists of US residents age 12 and older. In each year from 2004 to 2014, Substance Abuse and Mental Health Service Administration (SAMHSA) invited the sampled US residents age 12 and older to participate in NSDUH to assess drug-related behaviors and health topics. These individuals are from nationally representative samples drawn, recruited and assessed with informed consent/assent using multi-stage sampling. Annually, approximately 70,000 participants complete a multi-module audio-enhanced computer-assisted self-interview (ACASI), after review and approval by cognizant institutional review boards for the protection of human subjects in research (United States, 2015).

5.4.2 Study Sample

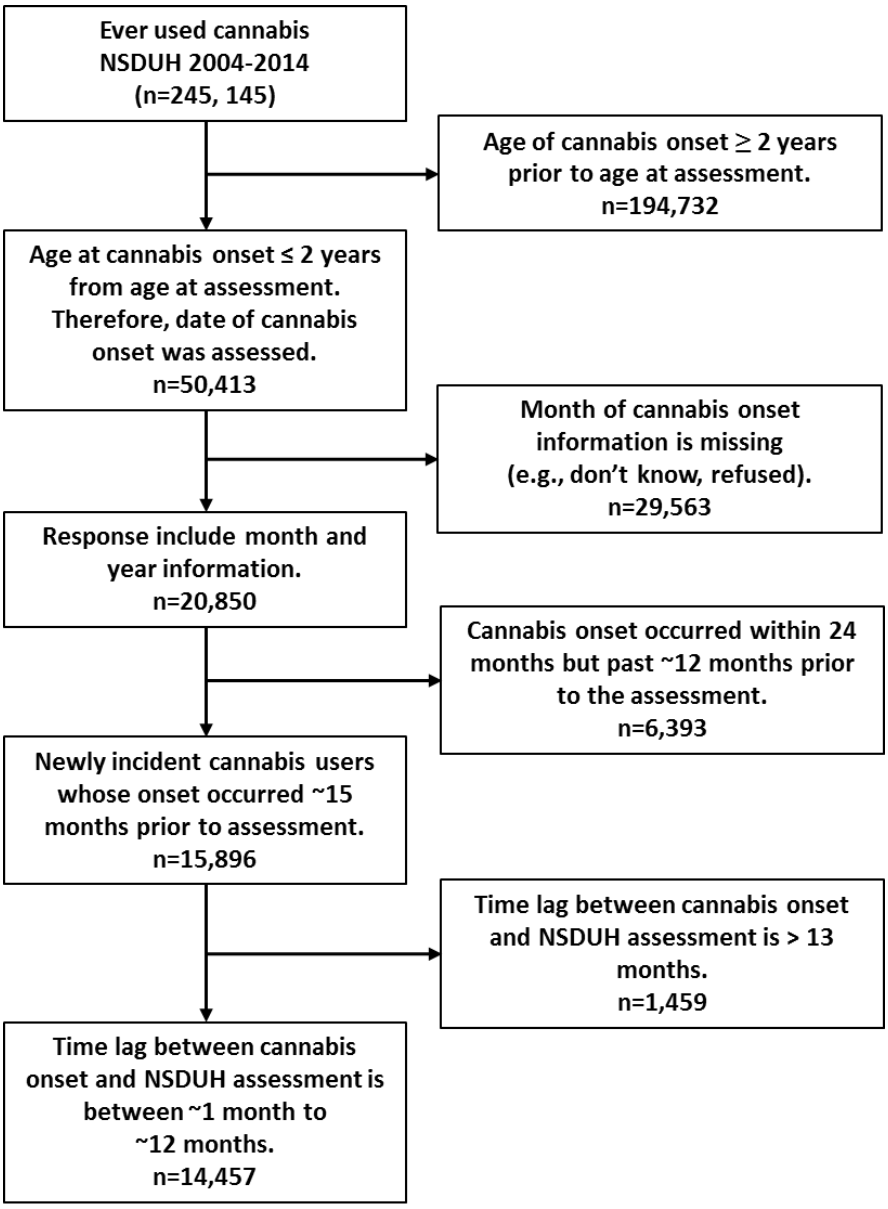
From NSDUH years 2004 to 2014, 15896 individuals were identified as cannabis users whose cannabis onset occurred within approximately 12 months (maximum of 15 months) prior to the NSDUH assessment. Of these newly incident cannabis users, 14457 individuals (>1100 each year) have the month and year information that is necessary to estimate the interval between cannabis onset and NSDUH assessment. Figure 5.1 shows a flowchart of the pre-specified criteria on how the analysis sample of 14457 for this study was obtained.

5.4.3 Assessment of the Key Response Variable

The key response variable is the onset of CUD-related experiences, measured in an ACASI module for cannabis users who has used cannabis at least 6 days within the past 12 months. The following are the 17 CUD-related experiences under study:

1. During the past 12 months, was there a month or more when you spent a lot of your time getting or using cannabis or hashish?
2. During the past 12 months, was there a month or more when you spent a lot of your time getting over the effects of the cannabis or hashish you used?
3. Were you able to keep to the limits you set, or did you often use cannabis or hashish more than you intended to?
4. During the past 12 months, did you need to use more cannabis or hashish than you used to in order to get the effect you wanted?
5. During the past 12 months, did you notice that using the same amount of cannabis or hashish had less effect on you than it used to?
6. During the past 12 months, did you want to or try to cut down or stop using cannabis or hashish?
7. During the past 12 months, were you able to cut down or stop using cannabis or hashish every time you wanted to or tried to?
8. During the past 12 months, did you have any problems with your emotions, nerves, or mental health that were probably caused or made worse by your use of cannabis or hashish?
9. Did you continue to use cannabis or hashish even though you thought it was causing you to have problems with your emotions, nerves, or mental health?
10. During the past 12 months, did you have any physical health problems that were probably caused or made worse by your use of cannabis or hashish?
11. Did you continue to use cannabis or hashish even though you thought it was causing you to have physical problems?

Figure 5.1. Flowchart of selecting valid sample. Data are from the National Surveys on Drug Use and Health, 2004-2014 (n=11,838 newly incident cannabis users).



12. During the past 12 months, did using cannabis or hashish cause you to give up or spend less time doing these types of important activities?
13. During the past 12 months, did using cannabis or hashish cause you to have serious problems like this either at home, work, or school?

14. During the past 12 months, did you regularly use cannabis or hashish and then do something where using cannabis or hashish might have put you in physical danger?
15. During the past 12 months, did using cannabis or hashish cause you to do things that repeatedly got you in trouble with the law?
16. During the past 12 months, did you have any problems with family or friends that were probably caused by your use of cannabis or hashish?
17. Did you continue to use cannabis or hashish even though you thought it caused problems with family or friends?

Reading through the list of questions presented in fixed sequence as survey items, it is possible to see that some of the items are explicit in their reference to what can legitimately called ‘problems’ (e.g., trouble with the law, which by the way is no longer included in the criteria for DSM-5 ‘cannabis addiction’). Due to this mixture of survey items about experiences and problems, in this study, the term ‘problem-experience’ is used to characterize the collection, abbreviated as ‘PE’. The term ‘symptom’ is avoided because there is no clinician’s cross-examination or interrogation to clarify which PE actually are ‘symptoms’ of an underlying pathological process (e.g., see J. C. Anthony et al. 1985). In addition, this approach avoids potentially unnecessary ‘medicalizing’ of human experiences that are not clearly pathological (Ivan Illich 1975).

5.4.4 Elapsed Time from Cannabis Onset to Assessment

Careful study of these standardized self-interview items can disclose that some of these experiences qualify as ‘cannabis problems’ such that there has been trouble for the user, or for others such as family members or teachers, or supervisors. But other experiences, in isolation, do not clearly qualify as ‘a problem’ per se. A prime example involves spending a lot of time

getting cannabis, which in isolation might not be a ‘problem’ for anyone. To call it a ‘problem’ when it occurs in isolation is to disregard social circumstances and developmental differences that would tend to create an unwanted source of variation in the epidemiological study of age-specific and geographical distributions and dynamics of cannabis involvement. As already mentioned, the 12-year-old with few cannabis-using friends might have to spend a lot of time getting the second supply of the product, relative to the older adolescent or adult user. In longitudinal study of cannabis involvement, this experience might dissipate, making it appear that the severity of cannabis dependence has declined as time passed. For this reason, our research group does not characterize this experience as a ‘problem’ unless we have other evidence that there is a problem. Occurring in an individual as the only ‘yes’ answer to these 17 questions, this experience certainly would not qualify as a ‘symptom’ of any underlying pathological process.

As for geographic variation, consider the ‘drug seeking time’ for the adult who lives next door to a cannabis shop in Denver versus another adult who lives in a Colorado county that bans cannabis sales, and for whom the nearest shop is an hour away by bus. The first most likely would not have to spend a lot of time getting cannabis, but the second would. Or consider two adults who live together, both meeting DSM-5 criteria for a cannabis use disorder, but with only two criteria met, one of which involves spending a lot of time getting cannabis. One of these two adults moves to Denver and chooses a home next door to a cannabis shop, while the other continues to take the bus several times each month. In a follow up study, the ‘mover’ will then be discovered to have a disorder ‘in remission’ because that diagnostic criterion is not fulfilled. The ‘stayer’s’ diagnosis remains active and intact.

In this study, the elapsed time since cannabis onset is measured using the month-by-month information after the month of cannabis first use, measured by the ACASI cannabis use module, relative to the quarter of NSDUH assessment. Cannabis use questions were as follows: "Have you ever, even once, used cannabis or hashish?" "How old were you the first time you used cannabis or hashish?" "Did you first use cannabis or hashish in [CURRENT YEAR-1], or [CURRENT YEAR]?" "In what month in [YEAR] did you first use cannabis or hashish?"

In this study, the concept of a lag-time is defined as the period from cannabis onset to survey assessment and is identified based on the timing information of cannabis onset and the timing of assessment in NSDUH survey data. Initially, the plan was to create 1-month lag-time intervals. However, publicly available NSDUH data are ones in which confidentiality of survey participants is protected by providing only month and year of drug onset, and quarter and year of survey assessment, which complicate the creation of the lag-time with equal lengths of intervals. An alternative approach taken in this study is to turn to an approximation of the intervals based on two assumptions. First, survey assessment was specified to have occurred at the mid-point of the middle month of the quarter (e.g., 15th of November for assessment occurring during the fourth quarter of the year). This assumption creates a problem for newly incident cannabis users who started during the month after the assumed month of onset. An example is when the onset of cannabis occurred in December when assessment has been specified to have occurred in November of the same calendar year. This reality prompted re-specification of an initial lag time interval in relation to the quarter of assessment such that the elapsed time since cannabis onset would be no more than three months, or "90 days." (A small error due to left-censoring occurs such that some of these newly incident cannabis users have a suppressed month of first use variable in the public use files in order to thwart re-identification of individuals — i.e., privacy

protection. This topic is discussed in the limitations section.) That is, the month of cannabis onset is any of the three months within the quarter of assessment. One implication is that the first lag-time interval is longer than the rest of the lag-time intervals. Table 5.1 shows the possible number of days for each lag-time. Second, it was assumed that drug onset occurred during the 15th of the month. The second assumption involves a specification that the 15th day of each month is used to calculate between-month intervals and lag times. For example, a user who started in January of the survey year and whose last use was in June is placed in the lag time interval based on Julian dates for January 15 and for June 15, even though actual start and dates might have been January 1 and June 30 (i.e., a half-month longer than the interval calculated using Julian dates for the 15th of each month. Appendix C Table 1-19 provides the proportion estimates of the occurrence of DSM-IV cannabis dependence and the occurrence individual cannabis-related problems and experiences across lag-times.

5.4.5 Statistical Analyses

A population-averaged model, sometimes called a marginal model, was used to estimate the within-subject correlation of the 17 key responses. Population-averaged models account for within-subject variation but do not explicitly account for the between-subject variation. In this study, a population-averaged model was used with generalized estimating equations (GEE), introduced by Liang and Zeger (1986), to account for the within-subject variation as opposed to the maximum likelihood approach for variance estimation of the more common generalized linear models. In GEE, parameters are estimated by specifying a link between the responses and covariates (e.g. log, identity), a variance function according to the assumed distribution of the responses (e.g., binomial) and the structure of the working correlation matrix (e.g., exchangeable). The regression coefficients are estimates of the marginal effects or "population-

Table 5.1. Approximated lag-time intervals from cannabis initiation to NSDUH survey assessment.

Lag-time	Approximated elapsed time under the assumptions* (days)	Range of elapsed times when assumptions are not applied (days)
1	30	0-90
2	60	1-120
3	90	30-150
4	120	60-180
5	150	90-210
6	180	120-240
7	210	150-270
8	240	180-300
9	270	210-330
10	300	240-360
11	330	270-390
12	360	300-420
13	390	330-450

* Assumptions: (1) survey assessment occurred during the mid-point of the middle month of the quarter; (2) drug onset occurred during the 15th of the month.

averaged" effects. Therefore, instead of individual-level inference as are obtained with subject-specific random effects models with ML, the inferences made from GEE coefficients are at the group level.

To establish a GEE model in the typical longitudinal study context, consider observations from n independent individuals. For each individual i, response y_{it} is obtained at times $t = 1, 2, 3, \ldots, p_i$, creating a p_i x 1 vector of responses, $Y_i = (y_{i1}, y_{i2}, y_{i3, \ldots}, y_{ip})$. For a covariate vector $x_{it} = (x_{it1}, x_{it2}, x_{it3, \ldots}, x_{itm})$, the expected marginal effect is $E(y_{it} \mid x_{it}) = \mu_{it}$. Given x_{it}, the variance of each of y_{it} is $\text{var}(y_{it}) = \phi v(\mu_{it})$, where ϕ is a scale parameter and $v(\cdot)$ is a known variance function. The working covariance matrix for y_{it} is $V_i = \phi A_i^{1/2} R(\alpha) A_i^{1/2}$, where $A_i = diag(v(\mu_{it}))$ *and* $R(\alpha)$ is the working correlation matrix. In this study, the main interest is to estimate y_{it}-to-y_{it} within-subject pairwise correlation. The correlation structure has been specified as unstructured in all of the population-averaged models. However, the subscript 't' stands for item numbers in the survey module, asked in sequence, one after the other during a matter of minutes, in contrast to

the standard longitudinal study context, with each ‘t’ standing for a different day-long or other interval after each assessment.

Some readers may be interested to know that Liang and Zeger worked out this application early in GEE development. It was applied in eye disease epidemiology, with t=1 and t=2 for two eyes of an individual, each with a state characterized separately on a single occasion (Katz, Zeger, and Liang 1994). In psychiatric epidemiology, it was applied by Liang and colleagues in a study of multiple individual clinical features of anxiety and mood disorders (Andrade, Eaton, and Chilcoat 1994). Since then, the Anthony research group has published a long series of drug research papers that have applied this method. It is covered in the most recent editions of the original Liang-Zeger-Diggle text on the GEE, and in the longitudinal analysis text by Fitzmaurice, Laird, and colleagues.

In this study, an intercept only model was fitted, making the expected marginal effect of $E(y_{it} |) = \mu_{it}$ for each NSDUH year. From the fitted model, there were 136 y_{it}-to-y_{it} within-subject pairwise correlation estimates from the p_i x p_i working correlation matrix for the item-level data. The standard errors of y_{it}-to-y_{it} correlation estimates are obtained without making distribution assumptions using the bootstrap approach. Then, the year-by-year correlation estimates and their standard errors are meta-analyzed to obtain a summary for 11 estimates of individual y_{it} from 11 NSDUH assessment years. The resulting number of within-subject pairwise correlation estimates is 136 for each lag-time interval.

To assess the trend of the within subject pairwise correlation estimates over strata defined by lag-time intervals of cannabis use, a longitudinal approach using linear mixed models (LMM) was used. In this approach, each pairwise combination of the 17 problems and experiences was considered as individual observation with 13 repeated outcome measures, one for each lag-time.

In the model, the predictors are lag-time dummy variables that were created from the lag-time variable with 13 values. The random-coefficient model is specified as:

$$PWWSC_{ij} = \beta_1 + \sum_{m=1}^{t-1} \beta_m Lagtime_{ij} + \varsigma_{1j} + \varsigma_{2j} Lagtime_{ij} + \varepsilon_{ij}$$

where $PWWSC_{ij}$ is the pairwise within-subject correlation, β_1 is the intercept of the fixed parameters and is interpreted as the predicted value for *PWWSC* for lag-time 1, $\sum_{m=1}^{t-1} \beta_m Lagtime_{ij}$ are the slopes of the fixed parameter lag-times (t=1, 2, 3, …, 13), ς_{1j} (random intercept) represents the deviation of lag-time *j*'s intercept from the mean intercept β_1, ς_{2j} (random slope) represents the deviation of lagtime *j*'s slope from the mean slope β_2, and ε_{ij} represents "random" differences among correlation estimates within each pairwise PE combination. The dependencies of within-subject measures are accounted for by assuming an autoregressive covariance structure of the within-subject covariance matrix. An unstructured correlation matrix was specified for the residual covariance matrix. All analyses in this study were conducted using Stata 14 (StataCorp. 2015). Appendix B shows a sample of the Stata program.

5.4.6 Data Management

In conducting the GLM intercept only model with GEE, the 11 independent cross-sectional NSDUH data flat files ('wide data,' one row per participant) were converted into long format (17 rows per participant, one for each cannabis experience question). That is, the rows in the long format represent indicators measured in sequence, one item after the other, as opposed to the conventional longitudinal data structure, in which rows represent time points of measurement, separated by more than the limited number of seconds it takes the participant to move from one item to the next.

Table 5.2. PE-specific frequencies of all newly incident cannabis users. Data are from National Survey on Drug Use and Health, 2004-2014 (n=14457 newly incident cannabis users).

Elapsed time	Cannabis-related Problems and Experiences[a]																
	PE1	**PE2**	**PE3**	**PE4**	**PE5**	**PE6**	**PE7**	**PE8**	**PE9**	**PE10**	**PE11**	**PE12**	**PE13**	**PE14**	**PE15**	**PE16**	**PE17**
1	81	46	23	18	24	9	14	22	20	7	17	8	7	8	5	8	10
2	188	78	43	26	26	8	29	30	18	12	26	15	12	15	4	19	13
3	190	99	59	57	36	30	36	49	35	14	45	18	16	6	4	15	20
4	263	142	79	71	69	32	54	61	52	27	59	37	21	9	4	26	17
5	280	160	92	71	58	41	60	60	55	22	65	41	23	28	10	19	20
6	256	137	89	76	67	45	48	47	53	19	52	29	8	20	12	10	26
7	319	202	108	84	82	43	69	87	67	24	60	31	27	20	3	27	19
8	333	216	122	94	80	55	70	78	71	22	63	37	19	23	10	26	25
9	272	188	115	70	58	44	56	43	61	37	60	36	18	15	11	19	25
10	305	209	112	87	70	53	66	68	49	29	56	24	20	20	3	16	14
11	301	232	113	94	65	57	83	63	64	39	65	39	10	30	8	30	22
12	247	165	103	71	53	41	36	52	44	19	43	20	7	18	9	18	20
13	294	251	145	87	77	49	54	63	66	39	64	34	15	25	12	22	27
Total[b]	3329	2125	1203	906	765	507	675	723	655	310	675	369	203	237	95	255	258

[a] Summing all the PE frequencies does not equal to the total sample due to the occurrence of more than one PE for each observation.

[b] PE1 = want or try to cut down or stop using cannabis; PE2 = spent more time getting or using cannabis; PE3 = needed more cannabis to get the same effect; PE4 = cannabis use causes problems with family and friends; PE5 = less activities because of cannabis use; PE6 = continued using cannabis despite emotional problems; PE7 = using cannabis and do dangerous activities; PE8 = using the same amount of cannabis but had less effect; PE9 = cannabis use causes serious problems at home or work or school; PE10 = not able to keep limits or use more cannabis; PE11 = cannabis use causes problems with emotions or nerves; PE12 = continued using cannabis despite emotional problems; PE13 = more time spend getting over the effects of cannabis; PE14 = cannabis use cause problems with the law; PE15 = continued to use cannabis despite physical problems; PE16 = not able to cut or stop using cannabis every time; PE17 = any physical problems caused or worsened by cannabis use.

5.5 Results

Table 5.2 presents the frequencies of newly incident cannabis users who experienced the problems and experiences within approximately 15 months prior to the NSDUH assessment for all 11 survey years combined. Irrespective of the lag-time interval, the most occurring PE is "want or try to cut down or stop using cannabis."

Almost a quarter of the newly incident cannabis users experienced this cannabis-related PE. It is also the most frequently occurring individual PE for each lag-time interval. The second most commonly occurring PE is "spent more time getting or using cannabis." Then, ranked in order of frequency, the top two PEs are followed by "needed more cannabis to get the same effect," "cannabis use causes problems with family and friends," and "less activities because of cannabis use."

Figure 5.2 shows the scatterplot of the 136 pairwise combinations of the 17 cannabis-related PEs for each of the 13 lag-time-strata of newly incident cannabis users (Fig. 5.2a-5.2m). (To be clear, each newly incident user is in one and only one lag-time stratum. This approach is akin to studying age-related variation across successive age strata, or studying the fossils seen in successive layers of rock. It is not a longitudinal approach as might be achieved by studying individuals who move from one lag-time interval to the next.) By visually examining the plots, changes in the estimates can be observed, especially for lag-times 2-13 relative the first lag-time. In lag-time 1 (Figure 5.2a), the pairwise correlation estimates of most pairwise combinations of PEs hover around zero correlation values. In lag-times 2-4 (Figure 5.2b-5.2d), point estimates apparently shifted upward, although the confidence intervals of many pairwise combinations of PEs capture zero correlation. In lag-times 5-13 (Figure 5.2e-5.2m), some point estimates are greater than zero, and the confidence intervals of the pairwise combinations of majority of the

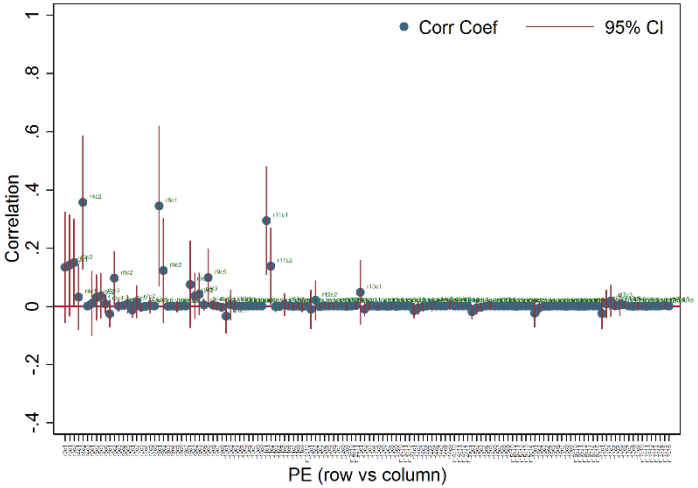
PEs do not capture the zero (null) correlation value. The increase in estimates seems most pronounced in lag-time 5.

A magnified view of these scatter plots in Figure 5.2 is presented in Figure 5.3, where the top 5 pairwise combinations with the highest point estimate in each lag-time is plotted. There are several noticeable trends of the most rapidly clustering CUD-related PEs. First, present from lag-time 2 to lag-time 13, the clustering of "want or try to cut down or stop using cannabis" and "spent more time getting using cannabis" is the one seen most frequently across the lag-times among the top 5 of the 136 combinations of PEs. This clustering also has the largest values for the first four lag-times (lag-time 1 to 4). Second, the next most occurring PE-to-PE combination is between "continued using cannabis despite emotional problems" and "continued use causes problems with family and friends." Interestingly, this clustering emerges at the top five at lag-times 3-13 and with the highest correlation estimates at lag-times 5, 6, 8, and 10 through 13. Third, the PE combination of "cannabis use causes problems with family and friends" and "spent more time getting or using cannabis" emerged from lag-time 1 to lag-time 7, except in lag-time 5. Fourth, by looking at the estimates visually, there seems to be an upward trajectory for the top 5 PE combinations from lag-time 1 to lag-time 13.

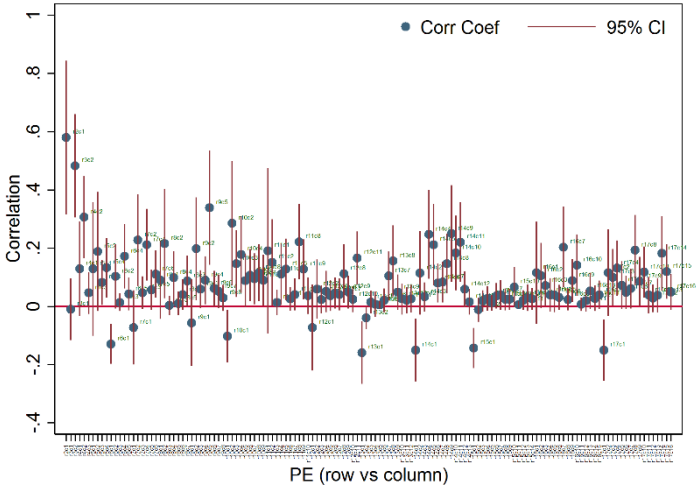
Alternatively, PE-to-PE relationship can be estimated using odds ratios, which, unlike correlation coefficients, are not margin-sensitive. Table 5.3 and 5.4 show the estimated odds ratios and their 95% confidence intervals respectively, comparing all possible pairs of the 17 CUD-related problems and experience within 1-90 days after cannabis onset. These estimates were obtained irrespective of lag-time strata because some strata had too few subjects.

Figure 5.2. Scatter plots of cannabis-related problems and experiences within-subject pairwise correlation estimates and their confidence intervals for each elapsed time interval: (a) lag-time 1 – (m) lag-time 13. Data are from NSDUH 2004-2014 (n=14457).

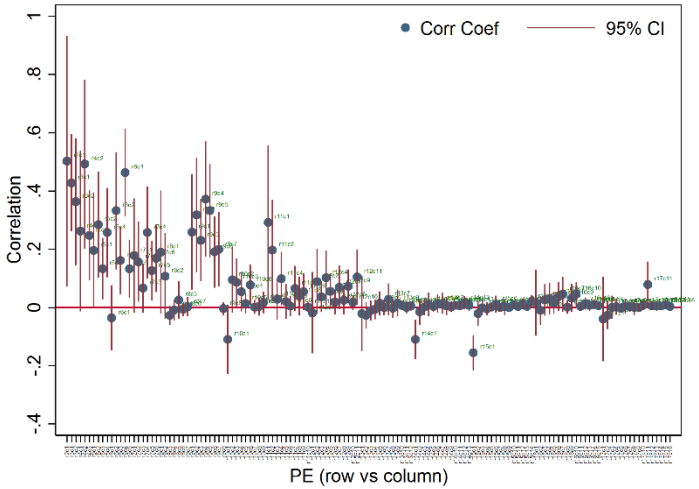
(a) Lag-time 1



(b) Lag-time 2



(c) Lag-time 3



(d) Lag-time 4

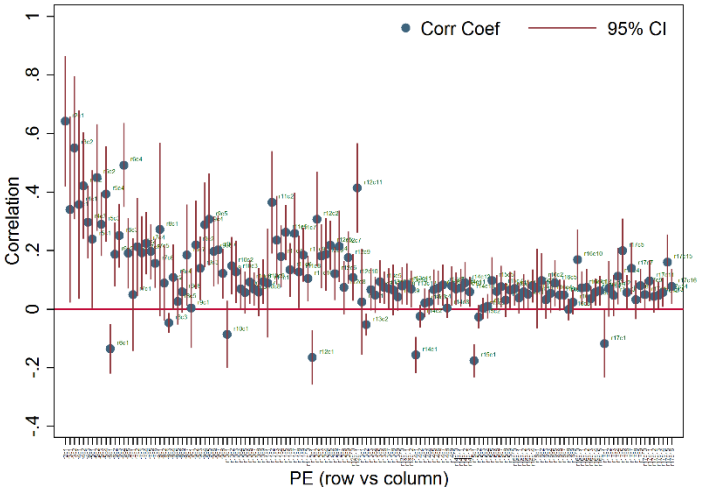
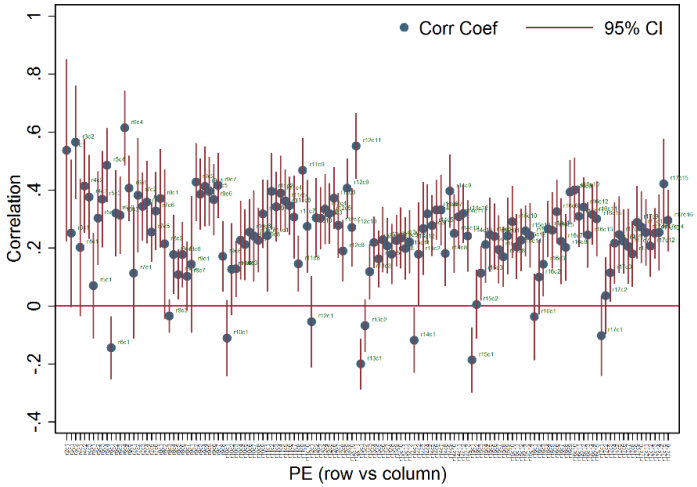
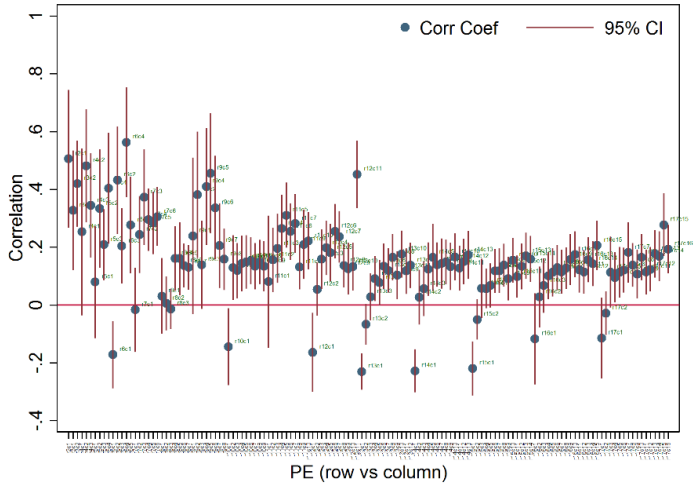


Figure 5.2 (cont'd)

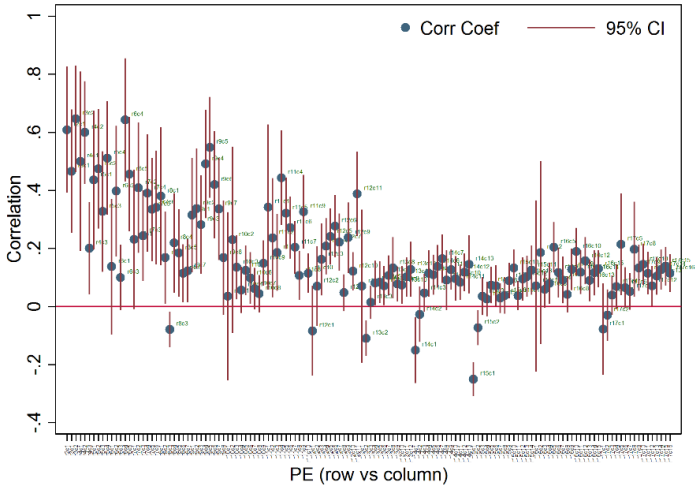
(e) Lag-time 5



(f) Lag-time 6



(g) Lag-time 7



(h) Lag-time 8

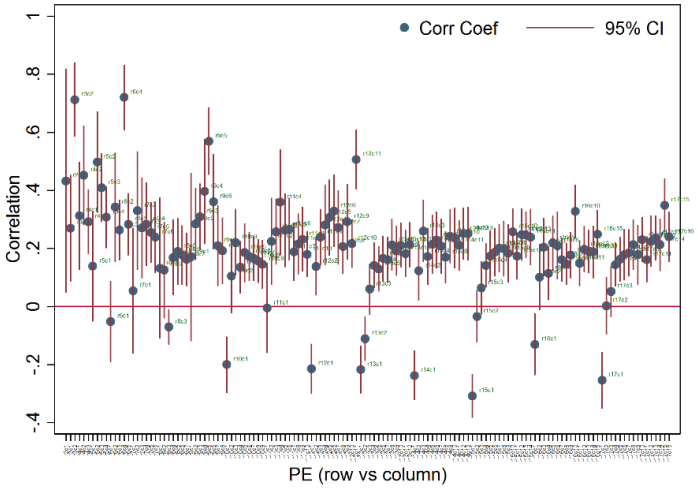
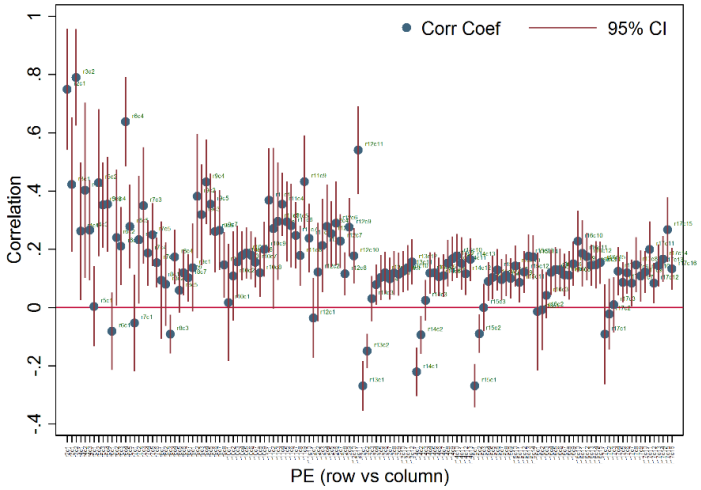
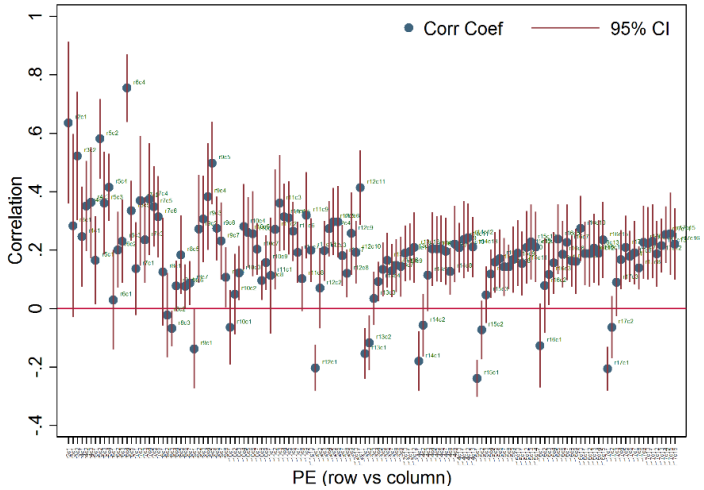


Figure 5.2 (cont'd)

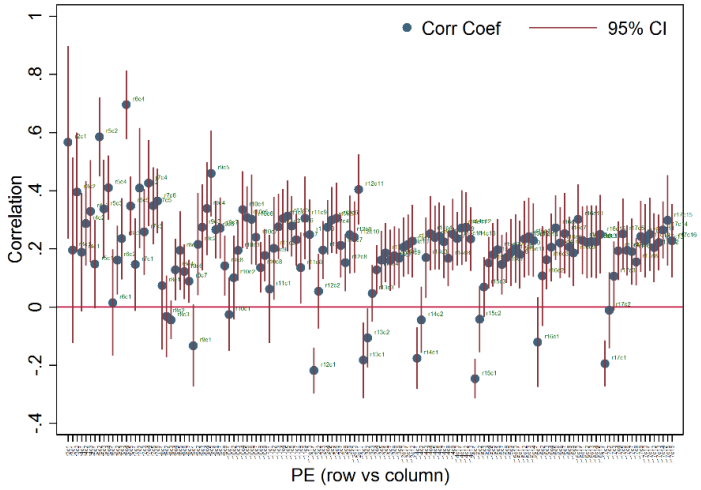
(i) Lag-time 9



(j) Lag-time 10



(k) Lag-time 11



(l) Lag-time 12

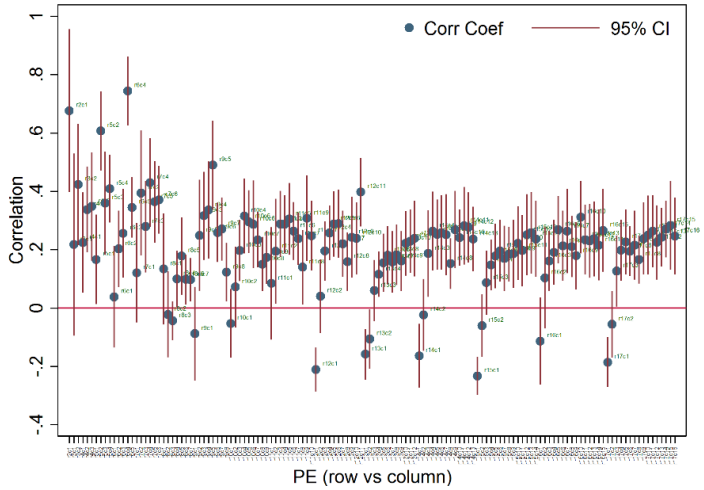


Figure 5.2 (cont'd)

(m) Lag-time 13

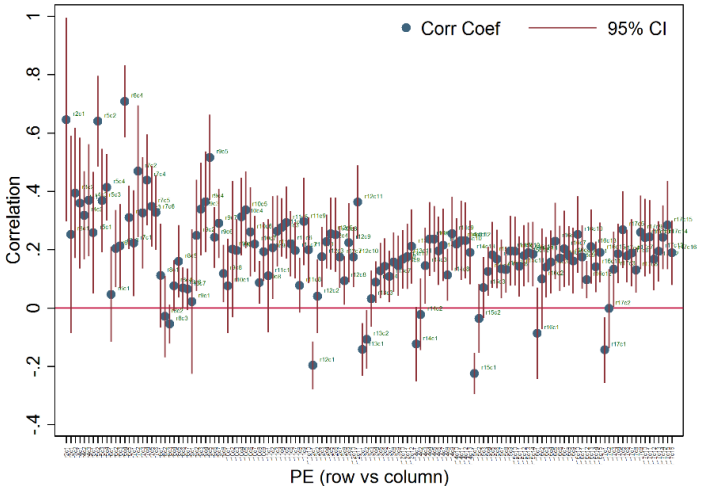
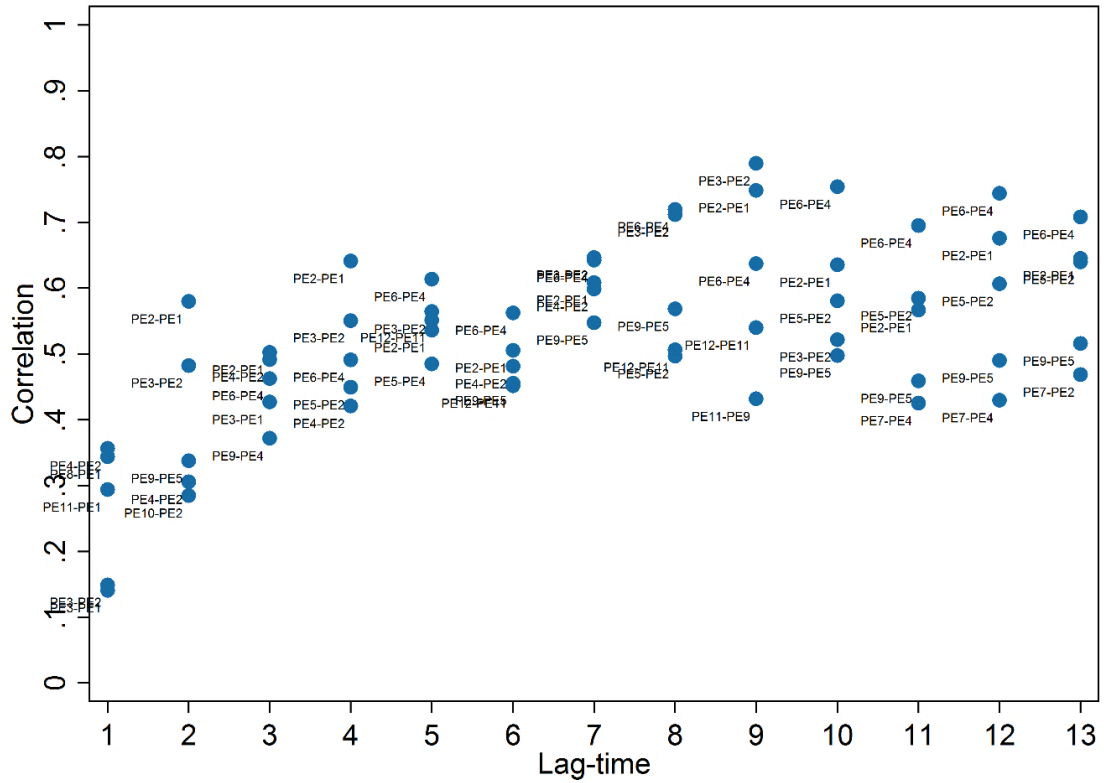


Figure 5.3. Top Five Pairwise PE combinations with highest point estimates of within-subject pairwise correlation in each lag-time.* Data are from NSDUH, 2004-2014 (n=14457 newly incident cannabis users).



*__PE1__ = want or try to cut down or stop using cannabis; __PE2__ = spent more time getting or using cannabis; __PE3__ = needed more cannabis to get the same effect; __PE4__ = cannabis use causes problems with family and friends; __PE5__ = less activities because of cannabis use; __PE6__ = continued using cannabis despite emotional problems; __PE7__ = using cannabis and do dangerous activities; __PE8__ = using the same amount of cannabis but had less effect; __PE9__ = cannabis use causes serious problems at home or work or school; __PE10__ = not able to keep limits or use more cannabis; __PE11__ = cannabis use causes problems with emotions or nerves; PE12 = continued using cannabis despite emotional problems; __PE13__ = more time spend getting over the effects of cannabis; __PE14__ = cannabis use cause problems with the law; __PE15__ = continued to use cannabis despite physical problems; __PE16__ = not able to cut or stop using cannabis every time; __PE17__ = any physical problems caused or worsened by cannabis use.

Table 5.3. Meta-analytic Summary Estimates of Odds Ratios Comparing Problems and Experiences Associated with Cannabis Use Disorder within 1-90 days after cannabis onset. Data are from the National Surveys on Drug Use and Health, 2004-2014 (n=3,710 newly incident cannabis users).

	(reference)																
	PE1	PE2	PE3	PE4	PE5	PE6	PE7	PE8	PE9	PE10	PE11	PE12	PE13	PE14	PE15	PE16	PE17
PE1																	
PE2	2.7																
PE3	2.7	3.3															
PE4	3.7	3.8	3.1														
PE5	3.3	4.6	3.5	3.9													
PE6	3.6	5.2	4.0	-	4.1												
PE7	2.9	3.9	3.3	4.0	3.8	4.7											
PE8	4.3	3.3	-	2.6	2.8	2.4	4.0										
PE9	4.1	4.8	4.2	4.0	5.8	4.8	4.6	3.2									
PE10	4.0	5.2	4.7	4.3	6.0	5.0	3.5	4.0	5.2								
PE11	4.2	3.6	2.9	3.3	3.5	3.6	3.5	3.2	4.3	3.2							
PE12	3.9	4.2	2.8	4.3	4.2	4.7	3.9	3.3	5.1	-	-						
PE13	4.2	-	-	3.1	4.2	0	5.4	4.2	4.6	2.7	5.7	2.9					
PE14	3.1	5.4	4.6	5.0	5.0	7.5	5.3	4.0	4.9	6.2	3.6	3.1	5.3				
PE15	-	4.3	4.3	3.6	4.5	-	4.4	-	4.3	5	4.4	-	3.8	4.9			
PE16	-	3.9	3.8	2.8	4.9	4.0	4.9	2.8	5.6	5.4	4.1	4.6	4.1	5.4	5.6		
PE17	3.0	3.3	3.7	3.8	3.6	4.5	4.6	3.2	3.2	4.1	4.1	-	3.6	4.7	-	4.5	

Note: "-" = not enough sample to estimate the odds ratio.

***PE1:** Wanted/Tried to cut down or stop using cannabis; **PE2:** Spent a lot of time getting or using cannabis; **PE3:** Needed more to get the same effect; **PE4:** Caused problems with family or friends; **PE5:** Spent less time doing important activities; **PE6:** Contd. use despite problems w/ family or friends; **PE7:** Used cannabis and did dangerous activities; **PE8:** Used the same amount but had less effect; **PE9:** Caused serious problem at home or work or school; **PE10:** Was not able to keep limits; **PE11:** Caused problems with emotions; **PE12:** Contd. use despite emotional problems; **PE13:** Spent a lot of time getting over effects; **PE14:** Caused repeated problems with the law; **PE15:** Contd. use despite physical problems; **PE16:** Was not able to cut or stop; **PE17:** Caused physical problems;

Table 5.4. Estimated 95% Confidence Intervals of the Meta-Analytic Summary Odds Ratio Estimates Comparing Problems and Experiences Associated with Cannabis Use Disorder with within the first 90 days of cannabis use. Data are from the National Surveys on Drug Use and Health, 2004-2014 (n=3710 newly incident cannabis users).

	PE1	**PE2**	**PE3**	**PE4**	**PE5**	**PE6**	**PE7**	**PE8**	**PE9**	**PE10**	**PE11**	**PE12**	**PE13**	**PE14**	**PE15**	**PE16**	**PE17**
PE1																	
PE2	2.2,3.2																
PE3	2.1,3.5	2.8,3.9															
PE4	3.0,4.6	3.2,4.5	2.4,4.0														
PE5	2.5,4.4	4.0,5.4	2.8,4.4	3.1,4.9													
PE6	2.5,5.1	4.3,6.2	3.1,5.2	-,-	3.1,5.4												
PE7	2.1,4.0	3.0,5.1	2.4,4.5	3.3,5.0	3.0,4.9	3.8,5.9											
PE8	3.1,6.1	2.6,4.1	-,-	1.5,4.4	1.8,4.2	0.3,20.5	2.8,5.5										
PE9	3.2,5.3	3.9,5.9	3.4,5.2	3.3,5.0	4.9,6.8	3.9,5.8	3.8,5.7	2.2,4.6									
PE10	2.6,6.2	3.9,7.0	3.6,6.3	3.1,6.0	4.5,8.0	3.5,7.1	1.8,6.7	2.6,6.2	3.3,8.1								
PE11	3.5,5.1	2.8,4.5	2.1,4.2	2.5,4.3	2.7,4.6	2.6,5.1	2.6,4.7	2.3,4.4	3.3,5.6	1.4,7.1							
PE12	2.8,5.5	3.2,5.4	1.6,5.1	3.2,5.6	2.9,6.1	3.5,6.3	2.6,5.7	2.1,5.0	3.8,6.9	-,-	-,-						
PE13	2.9,6.0	-,-	-,-	1.3,7.3	2.6,6.7	-,-	3.8,7.6	3.0,5.9	3.3,6.3	0.2,30.4	3.4,9.6	1.0,8.8					
PE14	1.2,7.9	3.3,8.8	3.2,6.6	3.6,7.0	3.7,6.9	5.1,10.9	4.0,6.9	2.4,6.6	3.8,6.5	4.5,8.5	2.4,5.5	1.4,7.3	3.7,7.4				
PE15	-,-	2.7,6.7	2.6,7.0	1.1,12	2.4,8.4	-,-	2.6,7.4	-,-	2.3,8.1	2.9,8.7	2.0,9.8	-,-	1.2,12.3	2.4,9.9			
PE16	0,0	3.0,5.2	2.9,5.1	1.6,4.9	3.2,7.4	2.7,5.7	3.7,6.5	0.7,10.7	4.3,7.3	3.8,7.8	2.4,7.0	3.0,7.1	2.6,6.5	4.0,7.2	3.3,9.7		
PE17	1.5,5.8	2.2,4.9	2.6,5.4	2.7,5.2	2.2,5.8	3.0,6.6	3.0,7.1	1.7,6.2	1.9,5.4	2.5,6.5	3.0,5.7	-,-	1.9,6.5	3.2,7.0	-,-	2.6,7.9	

Note: "**-**" = not enough sample to estimate the odds ratio.

***PE1:** Wanted/Tried to cut down or stop using cannabis; **PE2:** Spent a lot of time getting or using cannabis; **PE3:** Needed more to get the same effect; **PE4:** Caused problems with family or friends; **PE5:** Spent less time doing important activities; **PE6:** Contd. use despite problems w/ family or friends; **PE7:** Used cannabis and did dangerous activities; **PE8:** Used the same amount but had less effect; **PE9:** Caused serious problem at home or work or school; **PE10:** Was not able to keep limits; **PE11:** Caused problems with emotions; **PE12:** Contd. use despite emotional problems; **PE13:** Spent a lot of time getting over effects; **PE14:** Caused repeated problems with the law; **PE15:** Contd. use despite physical problems; **PE16:** Was not able to cut or stop; **PE17:** Caused physical problems;

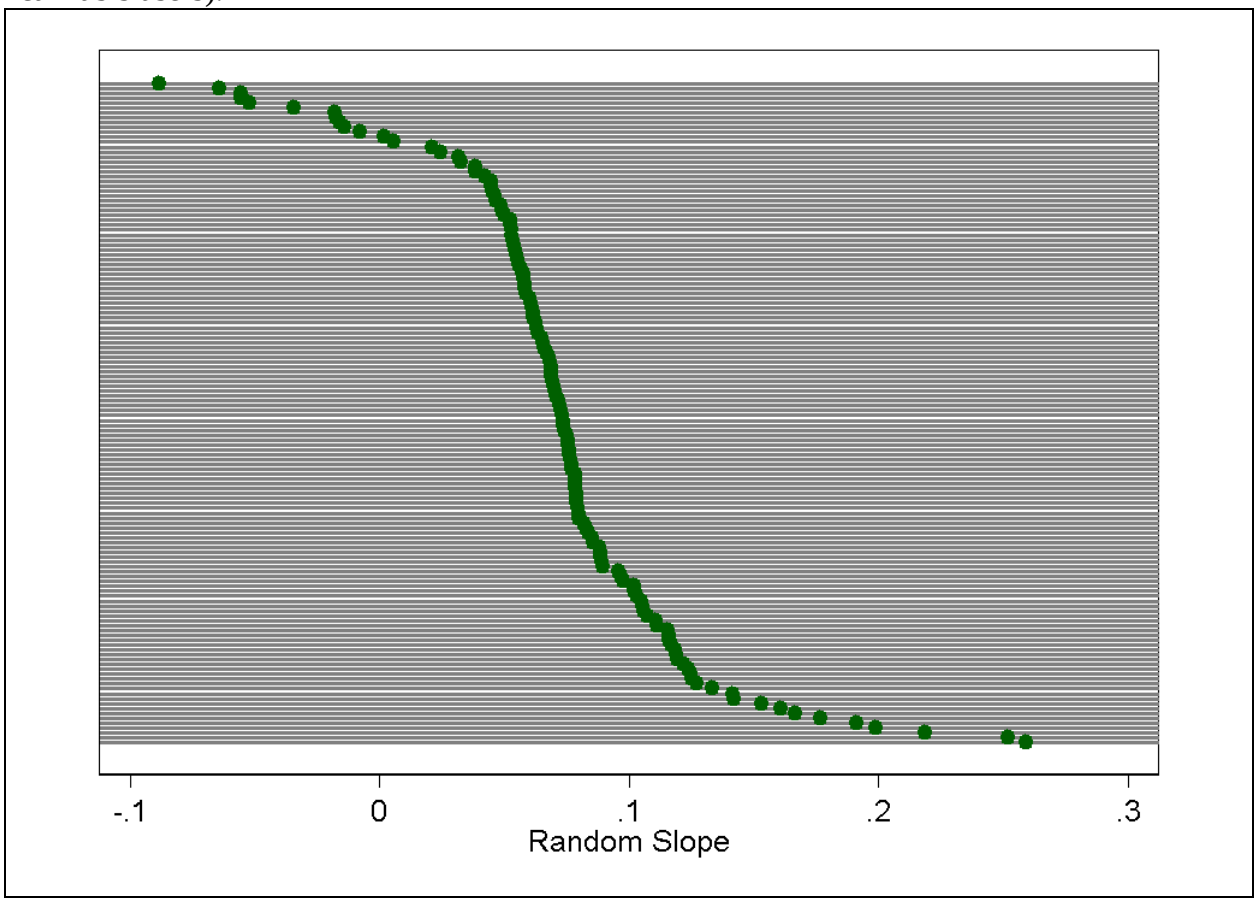
Table 5.5. Estimated relationship of pair-wise correlation of PE combinations and elapsed time from cannabis onset to NSDUH assessment using a linear mixed model. Data are from NSDUH, 2004-2014 (n=14457 newly incident cannabis users).

Parameter	**ß**	**95% CI**	**p-value**
Fixed Effects			
Lag-time1	(ref)	-	-
Lag-time2	0.064	0.050, 0.078	<0.001
Lag-time3	0.051	0.036, 0.067	<0.001
Lag-time4	0.103	0.087, 0.119	<0.001
Lag-time5	0.230	0.213, 0.247	<0.001
Lag-time6	0.137	0.120, 0.155	<0.001
Lag-time7	0.157	0.139, 0.175	<0.001
Lag-time8	0.180	0.161, 0.200	<0.001
Lag-time9	0.147	0.127, 0.168	<0.001
Lag-time10	0.170	0.148, 0.191	<0.001
Lag-time11	0.182	0.160, 0.204	<0.001
Lag-time12	0.188	0.165, 0.212	<0.001
Lag-time13	0.175	0.150, 0.200	<0.001
Intercept	0.156	-0.001, 0.033	0.072
Random Effects			
SD (lag)	0.010	0.010, 0.011	-
SD (Intercept)	0.073	0.062, 0.087	-
LR test vs. linear model: chi2(4) = 2108.25			Prob > chi2 < 0.0001

A more formal investigation of the changes of pairwise correlation estimates from lag-time 1 to lag-time 13 was conducted using linear mixed models, as described in the methods section. Table 5.6 shows the results from the linear mixed regression analysis. In this model, lag-times are considered as discrete (or categorical), with lag-time1 taken as the reference. The positive values of the ß coefficients suggest that the expected pair-wise correlation estimates for new users observed in strata for lag-times 2-13 are greater than can be seen for users in the stratum at lag-time 1. The differences are statistically significant, evidenced by the p-values of <0.001. Looking at the slope coefficients, the estimates increased from <0.1 beginning at lag-time 3 with the largest slope at lag-time 5, which is also visually apparent in Figure 5.2e when compared to other lag-times.

Turning to the random-effects parameters, there is evidence of variation across the PEs. The somewhat sizeable variance component on lag-time of 0.01 suggests that the influence of lag-time might vary across PEs. The variation can be visually examined as shown in Figure 5.4, based on an empirical Bayes approach that provides useful way to get a sense of how slopes vary across different pair combinations of CUD-related PEs. For this approach, a likelihood-ratio test was conducted to compare the current random slope model to a linear regression model, which does not include random components in the total variance component of the model. From the likelihood ratio test, the X^2 estimate with four degrees of freedom is 2108.25 and the p-value is <0.001, which is a departure from the null such that membership in lag-time strata matters and shows sub-group variation depending which PE is being studied.

Figure 5.4. Empirical Bayes Estimates of Random Slopes Across 136 Cannabis-related Problems and Experiences. Data are from NSDUH, 2004-2014 (n=14457 newly incident cannabis users).



In an exploration based on an assumption of lag-time strata that reflect a meaningful gradient of elapsed time since first cannabis use, linear mixed models were fitted with lag-time as a continuous variable for post-estimation analysis. Three models were fitted, with increasing dimension of the lag-time predictor. Table 5.6 presents the results of the three models. Irrespective of the dimension of lag-time, the results are consistent with the results when lag-time was treated as categorical. In Model 1, a positive slope of 0.0128 was observed with robust statistics ($p<0.05$). Prompted by this result, a nonlinear growth approach was conducted by squaring lag-time. From Model 2, the slope of lag-time squared is -0.0022 was observed with

Table 5.6. Results from Linear Mixed Models Predicting PE-to-PE Correlation Estimates Using Different Dimensions of the Lag-time Predictor. Data are the National Surveys on Drug Use and Health, 2004-20134 (n=14457 newly incident cannabis users).

	Model 1				Model 2				Model 3		
Parameter	**ß**	**95% CI**	**p-value**		**ß**	**95% CI**	**p-value**		**ß**	**95% CI**	**p-value**
Fixed Effects											
Intercept	0.0597	0.0456, 0.0737	<0.001		-0.0124	-0.0304, 0.0055	0.174		-0.0581	-0.0810. -0.0351	<0.001
Lag-time	0.0128	0.0110, 0.0147	<0.001		0.0434	0.0387, 0.0480	<0.001		0.0775	0.0658, 0.0891	<0.001
Lag-time^2					-0.0022	-0.0025, 0.0019	<0.001		-0.0081	-0.0100, -0.0062	<0.001
Lag-time^3									0.0003	0.0002, 0.0004	<0.001
Random Effects											
SD (intercept)	0.0556	0.0406, 0.0760	-		0.0715	0.0595, 0.0858	-		0.0740	0.0623. 0.0878	-
SD (slope)	0.0080	0.0063, 0.0102	-		0.0093	0.0078, 0.0110	-		0.0095	0.0080, 0.0117	-

robust statistics ($p<0.05$). Model 3 was then conducted by increasing the order of the lag-time into cubic. The slope lag-time cubic is 0.0003 with robust statistics ($p<0.05$).

5.6 Discussion and Conclusion

The main findings of this study can be summarized succinctly. First, this study found evidence of the increase in clustering of the problems and experiences as elapsed time from cannabis onset to survey assessment increases. Second, this study identified a set of what might emerge as rapidly clustering CUD-related PEs across durations from cannabis onset to assessment. Third, this study identified pairs of CUD-related PEs that co-occur persistently across multiple lag-times.

In terms of the most occurring CUD-related problems and experiences, the results are consistent to other published studies. Rosenberg and Anthony (2001) found using the Epidemiologic Catchment Area research that the most frequently occurring cannabis-related problems among cannabis users 18 years and older were "desire or fail to control use," followed by "spent time getting, using, recovering from cannabis intoxication" and "subjectively felt tolerance." Roxburgh et al. (2010) observed that difficulty controlling cannabis use was the most frequently occurring cannabis problem among student cannabis users age 12-17 in Australia. Dierker et al. (2017) reported that "an inordinate amount of time is occupied acquiring, using, or recovering from the effects" is the most frequently observed cannabis-related problem in the past 20 days of use among all active and prevalent cannabis users age 12-21 whose onset occurred 24 months prior to the NSDUH assessment. "Cut down," however, was the least frequent. As for the other findings, there has been no comparable research conducted prior to this study.

Several limitations of this study are worth noting. First, there are potential exchangeability issues introduced by the overlapping lag-times of cannabis use due to the lack of exact date of cannabis onset and the exact date of survey assessment in publicly available

NSDUH data. For example, the first lag-time overlaps with lag-times 2 to 5 as shown in Table 5.1. This limitation can be remedied by knowing a more refined date of the onset and the assessment. However, despite this potential exchangeability bias, difference in the average pair-wise correlation estimates for longer lag-times were found to be significantly higher than the average pair-wise correlation estimates at the first lag-time.

Second, the reported estimates of the observed CUD-related problems and experiences might be underestimated due to the discrete nature of the lag-times. The cross-sectional design does not capture the experience of cannabis users who did not survive in the prior interval (or during the same interval but did not survive prior to the assessment) with experiences that otherwise we may capture using carefully designed longitudinal approaches, in which time intervals are typically cumulative. However, the cross-sectional design provides a snapshot of the experience of cannabis users in the population in each lag-time stratum that might be useful in future research.

With respect to the NSDUH survey response rates, the annual response rates of the screening interview and the response rates of the main interview rates have been decreasing, resulting to a downward trend of the overall survey response rates (United States 2017a; Czajka and Beyler 2016). In 2016, the overall response rate is down to about 53%, from 72% in 2002. These levels of non-response can affect study estimates when nonresponse is associated with cannabis use. In addition, the extent to which this study's population-averaged estimates characterize the US study population might be affected by the magnitude of the non-response bias in NSDUH surveys.

As for other limitations, the findings of this study are subject to response errors due to the surveys' reliance on retrospective self-reports. These errors were reduced by limiting the

required time to recall the timing of cannabis onset and the occurrence CUD-related problems and experiences within the past 12 months. It is also important to note the possibility of underreporting cannabis-related behaviors, which reduces the validity of the findings reported in this study. Lastly, cannabis-related behaviors of individuals younger than age 12 are not captured in the survey. Although cannabis onsets before age 11 are rare, studying this younger age group will provide important findings to complement what is learned here.

With these limitations in mind, the findings may have several public health implications. First, there is a need to screen for newly cannabis use and early signs of CUD which might help to reduce the risk of CUD onset. The results of this study suggest that CUD-related problems and experiences begin to cluster as early as 90 days after cannabis onset, and this clustering tends to increase as we look across strata defined by increasing elapsed time since first cannabis use. These findings need to be further investigated through a carefully designed longitudinal study that assesses the experiences of newly incident cannabis users every month within the first 12 months of use. Second, as for diagnostic definitions, it might be beneficial to incorporate other cannabis-related problems and experiences to diagnose CUD. Further research is needed to investigate the heterogeneity of problems and experiences among cannabis dependents, which will then help us classify dependence cases based on the clustered experiences and investigate variations of cannabis-related outcomes such as recovery and recurrence of cannabis dependence (Farmer et al. 2015). Third, by understanding the problems and experiences that cluster together, clinicians may be able to identify the stage of the disorder and provide appropriate early interventions or treatment.

As for other future directions of this research, some might suggest looking for heterogeneity and for the sources of variation in clustering of cannabis-related experiences. For

example, frequency of use might be important. An increased occurrence of symptoms has been observed among newly incident cannabis users who use cannabis more often (Dierker et al. 2017). A stratified analysis based on frequency of cannabis use (e.g., daily vs. weekly) can be conducted. Also, there might be advantages in comparing the results reported here to those obtained from newly incident cannabis users who used cannabis on fewer than six days in the past year. The survey did not assess the CUD-related problems and experiences of these users. In terms of the recency of use, a post-estimation stratified analysis based on the recency of cannabis use (used in the past 30 days vs. last used past 30 days but within 12 months) was conducted but did not yield useful estimates due to very few newly incident cannabis users who did not use in the past 30 days before assessment. Second, results might vary across age groups (age 12-17 vs. age 18+) (Dierker et al. 2017), across varying THC doses (Bass and Martin 2000), and possibly across users with differing profiles of pre-existing illnesses or comorbidities (e.g., depression).

In summary, it is hoped that this research adds to our understanding of the natural history and course of cannabis experiences early in processes that govern whether and when a cannabis use disorder emerges. This study found evidence of increased clustering of CUD-related problems and experiences as duration of cannabis use increases using a novel approach. This work builds upon a very small body of prior evidence about problems and experiences that sometimes reflect symptoms of cannabis use disorder.

CHAPTER 6: SUMMARY, LIMITATIONS, AND IMPLICATIONS

6.1 Summary of Findings

Aggregated across the four manuscripts prepared as part of this dissertation research project, the main findings are as follows. In the first study, on the development of CUD-related problems and experiences, the main finding was that over three times greater odds of developing problems and experiences was observed among cannabis users who started using at least 1 IRD soon after cannabis onset compared to cannabis only users. The strongest associations were found for "spent a lot of time getting or using cannabis" and "needed more to get the same effect" for unweighted analysis and weighted analysis, respectively.

In the second study, on identifying latent classes of newly incident cannabis users, the main finding was that two latent classes of newly incident cannabis users (Class Cannabis+Analgesics and Class Cannabis+Hallucinogens) were identified after specification of "cannabis only" class (Class Cannabis Only). Relative to members of Class Cannabis Only, Class Cannabis+Analgesics members and Class Cannabis+Hallucinogens members have greater occurrence of cannabis dependence.

In the third study, the main finding was that increased co-variation of PE pairs was observed in longer elapsed time since onset of cannabis use. Some pairs of cannabis-related problems and experiences begin to show tangible co-variation as early as the first 90 days after first cannabis use. The most salient co-variation within individuals that early in the process of cannabis involvement involves: (1) "want or try to cut down or stop using cannabis;" (2) "spent more time getting or using cannabis;" (3) "needed more cannabis to get the same effect;" (4) "cannabis use causes problems with family and friends;" (5) "using the same among of cannabis but had less effect;" and (6) "cannabis use causes problems with emotions or nerves."

6.2 Limitations

Project-specific limitations were discussed in each study's discussion section (see sections 3.7, 4.6, and 6.7). Discussed here are limitations that are common across two or three studies. Many of the limitations are inherent to the NSDUH survey methodology.

A main concern is the temporal sequencing of IRD onset and the CUD-related outcomes. In study 1, the lack of the timing information of CUD-related problems and experiences created uncertainty in the order between IRD onset and the onset of CUD-related problems and experiences. It is, therefore, not clear whether IRD onset influenced the development of CUD-related PE or whether the CUD-related PE influenced the onset of IRD onset. As described in the discussion of Chapter 4, this temporal sequencing issue resulted into two possible interpretations of the results. A more complex possibility is when certain PE emerged prior to IRD onset, while the occurrence of other PE is influenced by the IRD onset. The temporal sequencing issue was also faced in study 2. There is lack of timing information of the onset of DSM-IV cannabis dependence.

With respect to the study design, the three studies are cross-sectional in nature. For causal inference, cross-sectional design is generally inferior to longitudinal study design. However, the findings of the three studies can serve as preliminary results that might help guide future longitudinal studies on the topic. With respect to the population under study, the NSDUH sampling frame excludes individuals younger than age 12. As a result, the estimates presented here do not reflect the occurrence of CUD-related problems and experiences for that younger population. Studying this younger age group might be an important population to focus on when trying to reduce the onset of cannabis, will provide important findings to complement what was observed here.

With respect to participation levels, the screening interview rates and the main interview rates show downward trend since around 2002, resulting in declining overall NSDUH response rates (from ~72% in 2002 and ~53% in 2016) (United States 2017a; Czajka and Beyler 2016). Drug use surveys generally face challenges related to non-response due to the sensitive topic of drug use and to the difficulty of reaching drug users. If nonresponse is associated with drug use (e.g., greater number of non-respondents among 'cannabis+IRD' users), high nonresponse rate affects the results of the studies reported here. With respect to the study samples, NSDUH survey sample frames did not include homeless individuals or transient people who did not live in shelters, resulting to potential underestimation of cannabis onset and the occurrence of CUD-related problems and experiences in the studies reported here.

With respect to the key response variables, the CUD-related problems and experiences of individuals age 12 and older are based on self-report response to standardized items. The self-report nature of the assessment might have introduced reporting errors in the results of the studies as NSDUH survey participants must recall their experiences over the past years prior to the assessment. Surveys on sensitive and stigmatized topics such as drug use face this challenge (Brener, Billy, and Grady 2003). These reporting errors are reduced by limiting the required time to recall the occurrence of CUD-related problems and experiences within the past 12 months. A similar issue was faced when recalling the timing of the onset of cannabis and other IRD.

Another important limitation is restriction of the study samples to the US and years under study. Cannabis products are diversifying, with increasing potency of unit. New forms of use such as vaping are becoming more common. The estimates based on the US in the years under study might not be generalizable, but at present, this study's estimates are the best available.

These limitations should be viewed in light of several strengths. First, the studies included in this dissertation have large sample sizes, which help improve the precision and external validity of the studies. Second, internal validity is improved in conducting the analysis year-by-year as opposed to conducting a pooled analysis. It is possible that survey participants might be different across NSDUH years. To avoid issues related to comparability of cases and controls (e.g., cases in 2014 compared with controls in 2004), the approach ensures that cases are paired with controls who were assessed during the same survey year. Also, this approach helps characterize the changes in drug-use related behaviors over the years. Third, the constant improvement of NSDUH survey methodology (e.g., ACASI) helps reduce variability and helps promote more accurate reporting of drug-related behaviors.

6.3 Implications and Future Directions

The findings reported in this study have several important implications. First, the evidence of increased risk of cannabis-related problems and experiences highlights the importance of preventing the onset of IRD among cannabis users, especially with the increasing prevalence of cannabis use in the US (Johnson et al. 2015; Hasin, Saha, et al. 2015b). It is important to conduct interventions that target the reduction of exposure to IRD among cannabis users. We might find them effective as those in the Netherlands, which started by segregating the cannabis market (MacCoun 2011).

Second, the timing of cannabis-related outcomes relative to the onset of cannabis is unknown. The strong associations found in the first study and the second study highlight the advantages of reducing the risk of starting to use other non-cannabis IRD soon after cannabis. For future investigations, explicit timing of cannabis-related problems and experiences will help shed some light on whether IRD use after cannabis onset increases the risk of the problems and

experiences or cannabis users seek other IRD to alleviate these symptoms of cannabis use disorder.

Third, the evidence of rapid co-occurrence of CUD-related problems and experiences soon after cannabis onset highlights the need of primary prevention that targets the escalation of use to CUD-related outcomes ("prevescalation") (e.g., Villanti et al. 2018). Such a preventative approach requires investigation of the trajectory of cannabis users since onset over refined time intervals. The month-to-month approach used in study 3 provides such information and found that strong covariation of problems and experiences occurred within the first 90 days from cannabis onset. This finding is especially important in relation to the occurrence of DSM-5 cannabis use disorder as the disorder requires co-occurrence at least two clinical features (see Table 2.1).

Fourth, the findings reported in the second study have important implications in identifying at-risk groups for future interventions and treatment strategy. The high abundant representation of analgesics users and hallucinogens users are worthy of investigation, might help unravel mechanistic actions to the occurrence of cannabis dependence among cannabis users in the US. Lastly, it is important to investigate the extent to which medical cannabis use contributes to the risk of cannabis dependence in the US as the availability of medical cannabis use increases (Hasin et al. 2017).

APPENDICES

Table A1. Mplus program for measurement equivalence between newly incident cannabis users whose onset occurred 1-6 months prior to the assessment and those whose onset occurred 7-12 months prior to the assessment.

	First six months	Second six months
MPLUS PROGRAM	TITLE: CFA DATA: FILE=I:\Polydrug\CF_All_drugs\MI\2014_NSDUH_Dataset_mi.csv; VARIABLE: NAMES ARE groupf6 poly cf1-cf17; USEVARIABLES = cf1-cf17; CATEGORICAL = cf1-cf17; MISSING ARE ALL (-9); USEO = (groupf6==1) ANALYSIS: ESTIMATOR=MLR; MODEL: F1 by cf1-cf17; OUTPUT: STANDARDIZED; MODINDICES;	TITLE: CFA DATA: FILE=I:\Polydrug\CF_All_drugs\MI\2014_NSDUH_Dataset_mi.csv; VARIABLE: NAMES ARE groupf6 poly cf1-cf17; USEVARIABLES = cf1-cf17; CATEGORICAL = cf1-cf17; MISSING ARE ALL (-9); USEO = (groupf6==0) ANALYSIS: ESTIMATOR=MLR; MODEL: F1 by cf1-cf17; OUTPUT: STANDARDIZED; MODINDICES;
MODEL FIT INFORMATION	Number of Free Parameters 34 Loglikelihood H0 Value -774.093 H0 Scaling Correction Factor for MLR 0.8949 Information Criteria Akaike (AIC) 1616.186 Bayesian (BIC) 1759.888 Sample-Size Adjusted BIC (n* = (n + 2) / 24) 1651.968 Chi-Square Test of Model Fit for the Binary and Ordered Categorical (Ordinal) Outcomes** Pearson Chi-Square Value 518.658 Degrees of Freedom 131026 P-Value 1.0000 Likelihood Ratio Chi-Square Value 136.654 Degrees of Freedom 131026 P-Value 1.0000	Number of Free Parameters 34 Loglikelihood H0 Value -1136.543 H0 Scaling Correction Factor for MLR 0.9585 Information Criteria Akaike (AIC) 341.086 Bayesian (BIC) 478.292 Sample-Size Adjusted BIC (n* = (n + 2) / 24) 370.401 Chi-Square Test of Model Fit for the Binary and Ordered Categorical (Ordinal) Outcomes** Pearson Chi-Square Value 695.215 Degrees of Freedom 131014 P-Value 1.0000 Likelihood Ratio Chi-Square Value 190.349 Degrees of Freedom 131014 P-Value 1.0000

Table A2. Measurement equivalence results, unweighted analysis and unweighted analysis.

UNWEIGHTED

						X^2 test of Model Fit		*X^2 test for Difference Testing*		WRMR	Decision
		# of par	RMSEA	CFI	TLI	*X^2 (df)*	p-value	*X^2 (df)*	p-value		
2014											Yes
	Configural	68	0.051	0.934	0.924	529.346 (238)	<0.001	-	-	2.294	
	Weak	52	0.054	0.923	0.918	591.548 (254)	<0.001	84.494 (16)	<0.001	2.641	
	Strong	36	0.052	0.924	0.923	605.047 (270)	<0.001	10.246 (16)	0.8535	2.651	
2013											Yes
	Configural	68	0.055	0.935	0.926	664.431 (238)	<0.001	-	-	2.644	
	Weak	52	0.051	0.941	0.936	646.994 (254)	<0.001	42.666 (16)	0.0003	2.784	
	Strong	36	0.050	0.940	0.940	663.618 (270)	<0.001	13.685 (16)	0.6222	2.797	
2012											No
	Configural	68	0.057	0.923	0.913	690.833 (238)	<0.001	-	-	2.609	
	Weak	52	0.052	0.933	0.928	650.610 (254)	<0.001	33.316 (16)	0.0067	2.717	
	Strong	36	0.050	0.932	0.932	670.927 (270)	<0.001	28.175 (16)	0.0301	2.746	
2011											No
	Configural	68	0.062	0.941	0.932	831.986 (238)	<0.001			2.890	
	Weak	52	0.059	0.944	0.940	819.734 (254)	<0.001	62.889 (16)	<0.001	3.080	
	Strong	36	0.057	0.943	0.942	844.720 (270)	<0.001	34.502 (16)	0.0046	3.112	
2010											Yes
	Configural	68	0.060	0.948	0.940	758.422 (238)	<0.001	-	-	2.814	
	Weak	52	0.058	0.948	0.945	766.219 (254)	<0.001	66.087 (16)	<0.001	3.005	
	Strong	36	0.056	0.948	0.948	784.417 (270)	<0.001	17.126 (16)	0.3775	3.020	
2009											Yes
	Configural	68	0.050	0.949	0.942	606.538 (238)	<0.001	-	-	2.420	
	Weak	52	0.052	0.943	0.939	666.799 (254)	<0.001	84.776 (16)	<0.001	2.726	
	Strong	36	0.050	0.942	0.942	687.124 (270)	<0.001	18.909 (16)	0.2734	2.745	
2008											Yes
	Configural	68	0.064	0.934	0.925	725.403 (238)	<0.001	-	-	2.701	
	Weak	52	0.059	0.941	0.936	694.892 (254)	<0.001	37.748 (16)	<0.0016	2.822	
	Strong	36	0.057	0.940	0.940	711.776 (270)	<0.001	21.026 (16)	0.1775	2.842	
2007*											No
	Configural	64	0.062	0.948	0.940	618.538 (208)	<0.001	-	-	2.651	
	Weak	49	0.062	0.944	0.940	666.071 (223)	<0.001	84.950 (15)	<0.001	2.908	
	Strong	34	0.061	0.943	0.943	691.738 (238)	<0.001	29.580 (15)	0.0135	2.940	
2006											-
	Configural	68	0.062	0.940	0.931	662.234 (238)	<0.001	-	-	2.393	
	Weak	52	0.058	0.943	0.939	653.492 (254)	<0.001	60.688 (16)	<0.001	2.688	

Table A2 (cont'd)

	Strong	36	0.057	0.942	0.942	674.441 (270)	<0.001	-	-	2.719	
2005											Yes
	Configural	68	0.069	0.920	0.908	774.661 (238)	<0.001	-	-	2.873	
	Weak	52	0.064	0.926	0.920	752.745 (254)	<0.001	45.630 (16)	0.0001	3.004	
	Strong	36	0.062	0.926	0.925	767.477 (270)	<0.001	15.652 (16)	0.4775	3.018	
2004											No
	Configural	68	0.061	0.948	0.941	656.27 (238)	<0.001	-	-	2.627	
	Weak	52	0.061	0.945	0.941	701.11 (254)	<0.001	85.23 (16)	<0.001	2.865	
	Strong	36	0.060	0.943	0.943	729.57 (270)	<0.001	40.88 (16)	0.0006	2.906	
Weighted											
2014											Yes
	Configural	68	0.035	0.962	0.957	370.44 (238)	<0.001	-	-	1.794	
	Weak	52	0.040	0.945	0.942	444.53 (254)	<0.001	78.54 (16)	<0.001	2.259	
	Strong	36	0.039	0.946	0.946	457.05 (270)	<0.001	11.50 (16)	0.7777	2.271	
2013											Yes
	Configural	68	0.035	0.942	0.934	412.08 (238)	<0.001	-	-	2.040	
	Weak	52	0.035	0.941	0.936	433.61 (254)	<0.001	45.30 (16)	0.0001	2.301	
	Strong	36	0.033	0.941	0.940	448.84 (270)	<0.001	16.06 (16)	0.4491	2.318	
2012											No
	Configural	68	0.059	0.840	0.817	720.50 (238)	<0.001	-	-	2.950	
	Weak	52	0.057	0.841	0.829	735.00 (254)	<0.001	88.56 (16)	<0.001	3.249	
	Strong	36	0.055	0.840	0.839	752.60 (270)	<0.001	40.08 (16)	0.0008	3.287	
2011											No
	Configural	68	0.050	0.928	0.918	618.38 (238)	<0.001	-	-	2.793	
	Weak	52	0.070	0.849	0.838	1051.39 (254)	<0.001	576.12 (16)	<0.001	4.080	
	Strong	36	0.069	0.844	0.843	1093.18 (270)	<0.001	97.74 (16)	<0.001	4.157	
2010											Yes
	Configural	68	0.036	0.936	0.927	424.609 (238)	<0.001	-	-	2.132	
	Weak	52	0.038	0.926	0.920	472.161 (254)	<0.001	73.49 (16)	<0.001	2.387	
	Strong	36	0.036	0.927	0.926	484.287 (270)	<0.001	16.39 (16)	0.4258	2.405	
2009											Yes
	Configural	68	0.037	0.940	0.932	435.961 (238)	<0.001	-	-	2.104	
	Weak	52	0.037	0.935	0.931	469.145 (254)	<0.001	53.84 (16)	<0.001	2.322	
	Strong	36	0.036	0.935	0.934	486.038 (270)	<0.001	23.19 (16)	0.1088	2.350	
2008											No
	Configural	68	0.070	0.900	0.886	824.344 (238)	<0.001	-	-	3.071	
	Weak	52	0.068	0.900	0.892	844.772 (254)	<0.001	91.22 (16)	<0.001	3.325	
	Strong	36	0.066	0.900	0.899	857.513 (270)	<0.001	32.05 (16)	0.0099	3.354	

Table A2 (cont'd)

2007*											Yes
	Configural	64	0.046	0.942	0.933	433.906 (208)	<0.001	-	-	2.242	
	Weak	49	0.045	0.941	0.937	453.037 (223)	<0.001	46.30 (15)	<0.001	2.414	
	Strong	34	0.043	0.942	0.941	466.183 (238)	<0.001	15.70 (15)	0.4023	2.432	
2006											-
	Configural	-	-	-	-	-	-	-	-	-	-
	Weak	-	-	-	-	-	-	-	-	-	-
	Strong	-	-	-	-	-	-	-	-	-	-
2005											Yes
	Configural	68	0.041	0.938	0.929	424.085 (238)	<0.001	-	-	2.056	
	Weak	52	0.062	0.846	0.835	713.948 (254)	<0.001	276.07 (16)	<0.001	3.248	
	Strong	36	0.060	0.845	0.844	733.741 (270)	<0.001	25.99 (16)	0.0542	3.268	
2004											Yes
	Configural	68	0.052	0.911	0.896	539.928 (234)	<0.001	-	-	2.423	
	Weak	52	0.056	0.890	0.883	628.940 (254)	<0.001	127.02 (16)	<0.001	2.948	
	Strong	36	0.054	0.890	0.889	646.204 (270)	<0.001	25.86 (16)	0.0561	2.974	
Accounting for complex sampling:											
						X^2 test of Model Fit		*X^2 test for Difference Testing*		WRMR	Decision
		# of par	RMSEA	CFI	TLI	*X^2 (df)*	p-value	*X^2 (df)*	p-value		
2014											Yes
	Configural	68	0.035	0.962	0.957	370.441 (238)	<0.001	-	-	1.794	
	Weak	52	0.040	0.945	0.942	444.527 (254)	<0.001	78.54 (16)	<0.001	2.259	
	Strong	36	0.039	0.946	0.946	457.046 (270)	<0.001	11.50 (16)	0.7777	2.271	
2013											Yes
	Configural	68	0.035	0.942	0.934	412.080 (238)	<0.001	-	-	2.040	
	Weak	52	0.035	0.941	0.936	433.607 (254)	<0.001	45.30 (16)	0.0001	2.301	
	Strong	36	0.033	0.941	0.940	448.835 (270)	<0.001	16.06 (16)	0.4491	2.318	
2012											No
	Configural	68	0.059	0.840	0.817	720.498 (238)	<0.001	-	-	2.950	
	Weak	52	0.057	0.841	0.829	734.995 (254)	<0.001	88.556 (16)	<0.001	3.249	
	Strong	36	0.055	0.840	0.839	752.601 (270)	<0.001	40.081 (16)	0.0008	3.287	
2011											No
	Configural	68	0.050	0.928	0.918	618.379 (238)	<0.001	-	-	2.793	
	Weak	52	0.070	0.849	0.838	1051.385 (254)	<0.001	576.122 (16)	<0.001	4.080	
	Strong	36	0.069	0.844	0.843	1093.181 (270)	<0.001	97.743 (16)	<0.001	4.157	

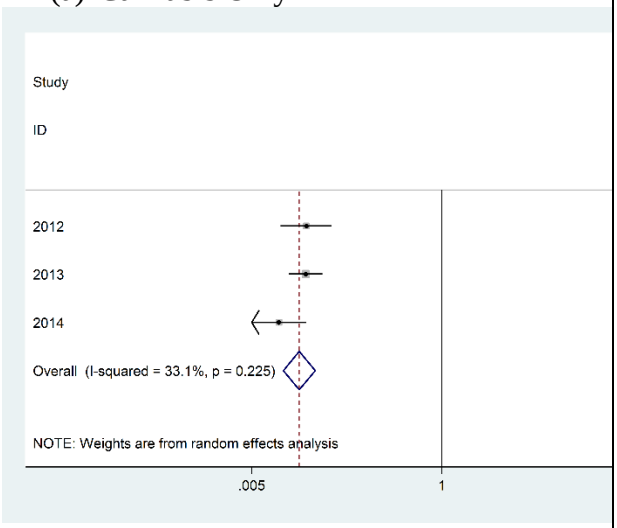
Table A2 (cont'd)

2010											Yes
	Configural	68	0.036	0.936	0.927	424.609 (238)	<0.001	-	-	2.132	
	Weak	52	0.038	0.926	0.920	472.161 (254)	<0.001	73.491 (16)	<0.001	2.387	
	Strong	36	0.036	0.927	0.926	484.287 (270)	<0.001	16.394 (16)	0.4258	2.405	
2009											Yes
	Configural	68	0.037	0.940	0.932	435.961 (238)	<0.001	-	-	2.104	
	Weak	52	0.037	0.935	0.931	469.145 (254)	<0.001	53.835 (16)	<0.001	2.322	
	Strong	36	0.036	0.935	0.934	486.038 (270)	<0.001	23.187 (16)	0.1088	2.350	
2008											No
	Configural	68	0.070	0.900	0.886	824.344 (238)	<0.001	-	-	3.071	
	Weak	52	0.068	0.900	0.892	844.772 (254)	<0.001	91.218 (16)	<0.001	3.325	
	Strong	36	0.066	0.900	0.899	857.513 (270)	<0.001	32.047 (16)	0.0099	3.354	
2007*											Yes
	Configural	64	0.046	0.942	0.933	433.906 (208)	<0.001	-	-	2.242	
	Weak	49	0.045	0.941	0.937	453.037 (223)	<0.001	46.300 (15)	<0.001	2.414	
	Strong	34	0.043	0.942	0.941	466.183 (238)	<0.001	15.700 (15)	0.4023	2.432	
2006											-
	Configural	-	-	-	-	-	-	-	-	-	
	Weak	-	-	-	-	-	-	-	-	-	
	Strong	-	-	-	-	-	-	-	-	-	
2005											Yes
	Configural	68	0.041	0.938	0.929	424.085 (238)	<0.001	-	-	2.056	
	Weak	52	0.062	0.846	0.835	713.948 (254)	<0.001	276.066 (16)	<0.001	3.248	
	Strong	36	0.060	0.845	0.844	733.741 (270)	<0.001	25.988 (16)	0.0542	3.268	
2004											Yes
	Configural	68	0.052	0.911	0.896	539.928 (234)	<0.001	-	-	2.423	
	Weak	52	0.056	0.890	0.883	628.940 (254)	<0.001	127.022 (16)	<0.001	2.948	
	Strong	36	0.054	0.890	0.889	646.204 (270)	<0.001	25.854 (16)	0.0561	2.974	

APPENDIX B: Sample Description and Risk Estimates Cannabis Dependence

Table B1. Sample Description and Risk Estimates of Cannabis Dependence for Cannabis+IRD Subgroups. Data are from the US National Surveys on Drug Use and Health, 2012-2014 (n= 3283 newly incident cannabis users).

(a) Cannabis Only



(b) Cannabs_IRD

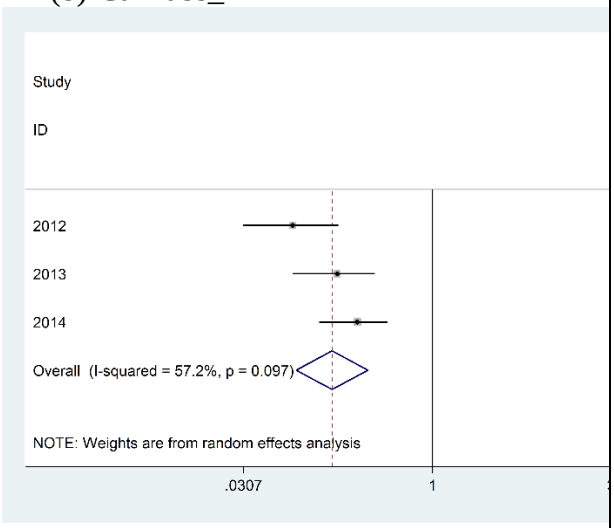


Table B2. Sample Description and Risk Estimates of Cannabis Dependence for Cannabis+IRD Subgroups. Data are from the US National Surveys on Drug Use and Health, 2012-2014 (n= 3283 newly incident cannabis users).

			DSM-IV Cannabis Dependence IRD-specific pooled estimate			
	Total		Unweighted		Weighted	
Cannabis + IRD	n	n	%	95% CI	%	95% CI
+*Cocaine*	12	2	16.7	3.3, 54.3	30.4	7.0, 71.6
+*Stimulants*[a]	35	4	11.4	4.1, 27.8	13.4	4.0, 36.5
+*Pain Reliever*[b]	93	17	18.3	11.6, 27.7	19.0	10.6, 31.8
+*Ecstasy*	36	4	11.1	4.0, 27.1	5.6	1.0, 25.8
+*Hallucinogens*[c]	73	12	16.4	9.5, 27.1	15.6	6.2, 33.8
+*LSD*	19	3	15.8	4.6, 42.2	20.7	3.8, 63.1
+*Anxiolytics*	32	6	18.8	8.3, 37.1	30.3	11.6, 58.8
+*Inhalants*	48	9	18.8	9.8, 32.9	27.4	10.5, 54.8
+*Sedatives*	6	1	16.7	0.9, 81.4	20.2	1.6, 80.1

[a] includes Methamphetamine;

[b] includes Heroin and OxyContin
[c] includes PCP.

Of the 3284 NICU, 229 have started using at least one non-cannabis IRD soon after the onset of cannabis within the 12-month interval. The meta-analytic summary risk estimates of developing DSM-IV cannabis dependence is 2.2% (95% CI = 1.7%, 2.8%) for 'cannabis only' users and 14.0% (95% CI = 10.0%, 19.1%) for 'cannabis+IRD' users. Weighted to the US population, these estimates are 1.9% (95% CI = 1.2%, 2.9%) for cannabis only users and 15.7% (95% CI = 8.1%, 30.4%) for cannabis+IRD users. For both weighted and unweighted estimates, the non-overlapping confidence intervals suggest that the difference between the two groups are statistically robust. Table B2 shows the IRD-specific pooled weighted and unweighted estimates for cannabis+IRD subgroups. For both weighted and unweighted estimates, there was no statistically significant risk difference among the subgroups, indicated by the overlapping confidence intervals.

APPENDIX C: Risk Estimates of Drug-Related Outcomes Over Elapsed Time of Cannabis Use

Figure C1. Meta-analytic Summary Proportion Estimates of the Occurrence of DSM-IV Cannabis Dependence Over Lag-time Intervals. Data are from National Surveys on Drug Use and Health, 2004-2014 (n=14,457).

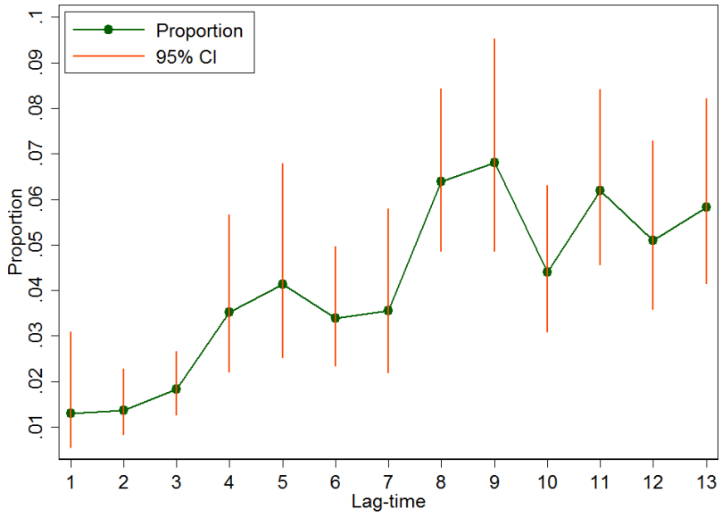


Figure C2. Meta-analytic summary proportion estimates of using at least 1 IRD soon after cannabis over lag-time intervals. Data are from National Surveys on Drug Use and Health, 2004-2014 (n=14,457).

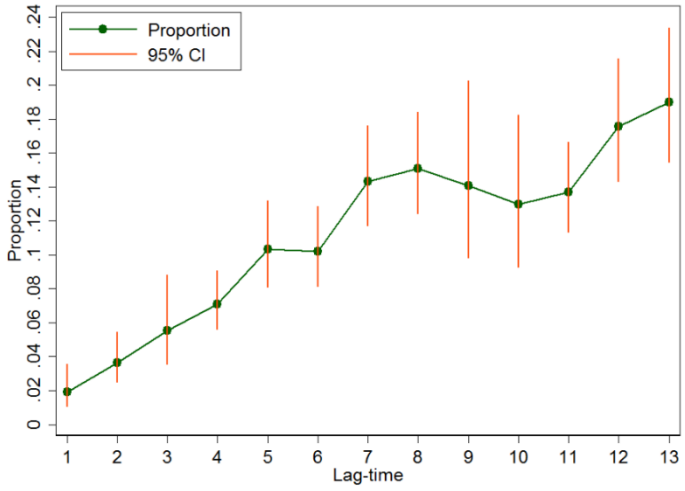


Figure C3. Meta-analytic summary proportion estimates of using at least 2 IRD soon after cannabis over lag-time intervals. Data are from National Surveys on Drug Use and Health, 2004-2014 (n=14,457).

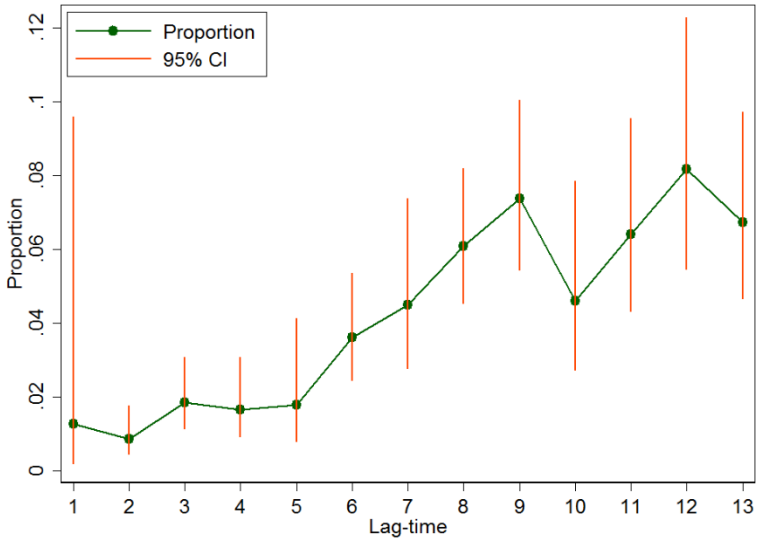


Figure C4. Meta-analytic summary proportion estimates of using at least 3 IRD soon after cannabis over lag-time intervals. Data are from National Surveys on Drug Use and Health, 2004-2014 (n=14,457).

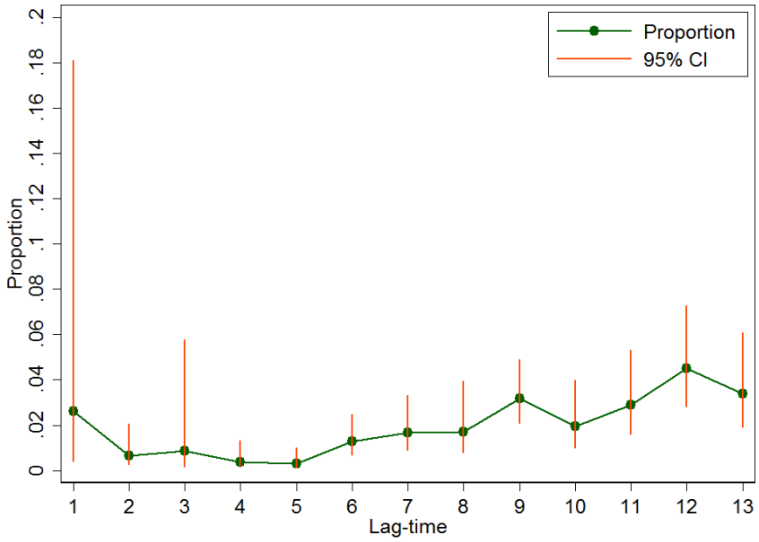


Figure C5. Meta-analytic summary proportion estimates of using at least 4 IRD soon after cannabis over lag-time intervals. Data are from National Surveys on Drug Use and Health, 2004-2014 (n=14,457newly incident cannabis users).

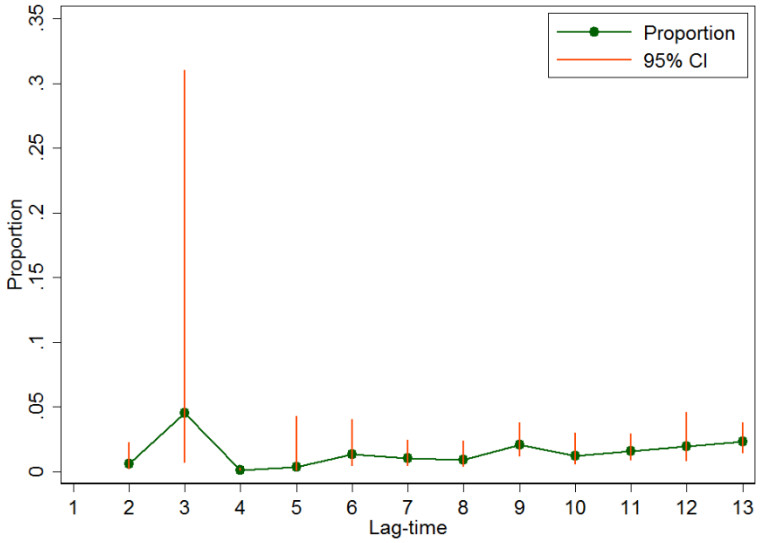


Figure C6. Meta-analytic summary proportion estimates of using cannabis at least 6 days in the past year over lag-time intervals. Data are from National Surveys on Drug Use and Health, 2004-2014 (n=14,457newly incident cannabis users).

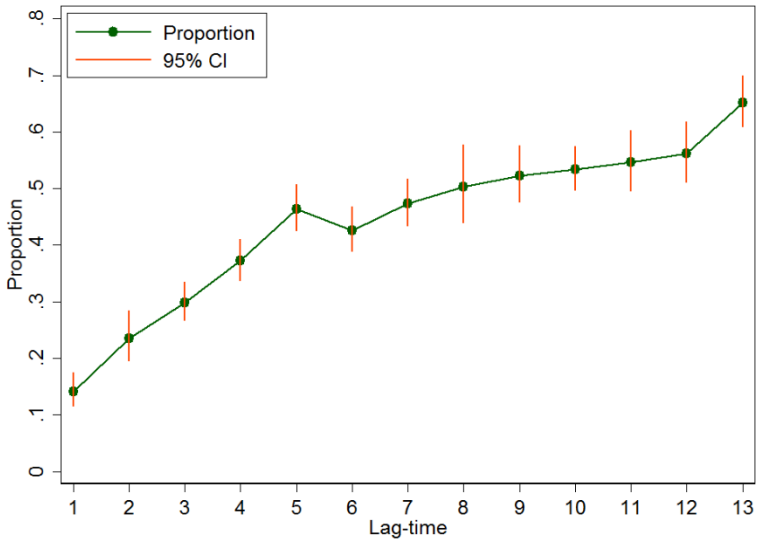


Figure C7. Meta-analytic summary proportion estimates of the occurrence of cannabis use disorder over lag-time intervals. Data are from National Surveys on Drug Use and Health, 2004-2014 (n=14,457newly incident cannabis users).

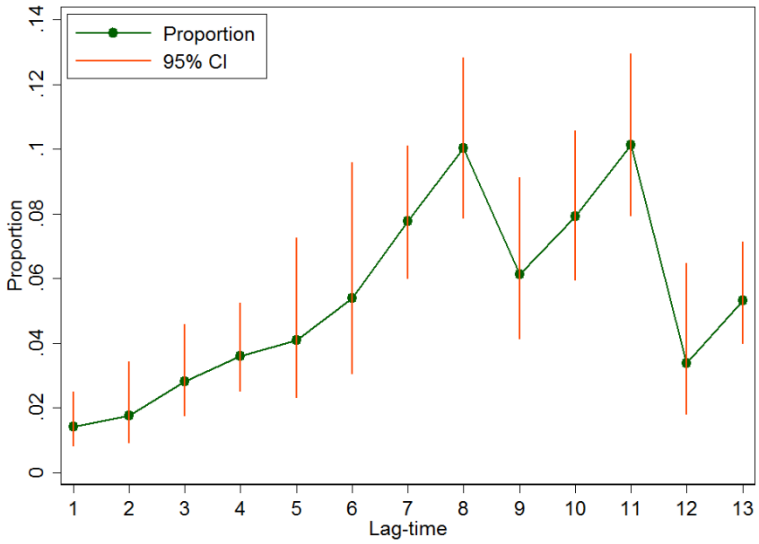


Figure C8. Meta-analytic summary proportion estimates of cocaine onset soon after cannabis onset over lag-time intervals. Data are from National Surveys on Drug Use and Health, 2004-2014 (n=14,457newly incident cannabis users).

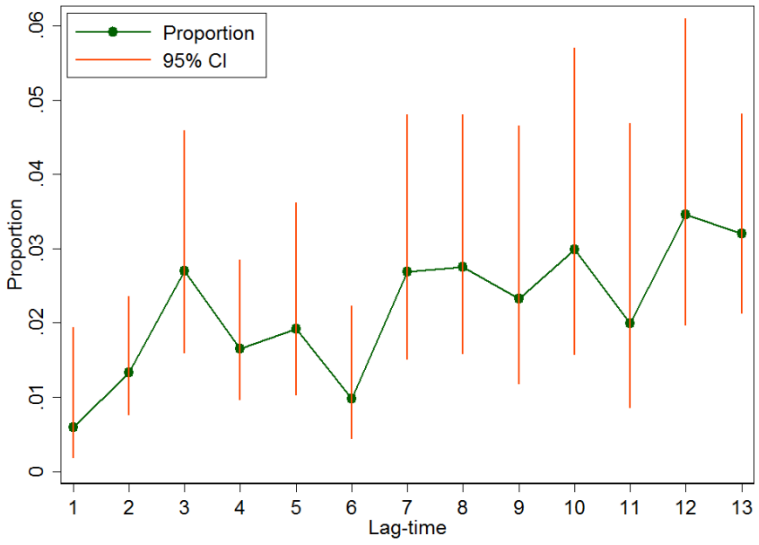


Figure C9. Meta-analytic summary proportion estimates of heroin onset soon after cannabis onset over lag-time intervals. Data are from National Surveys on Drug Use and Health, 2004-2014 (n=14,457 newly incident cannabis users).

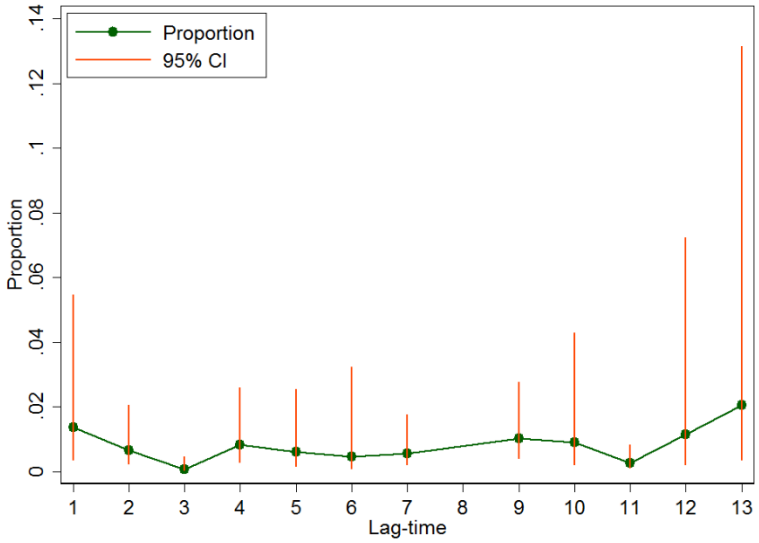


Figure C10. Meta-analytic summary proportion estimates of inhalants onset soon after cannabis onset over lag-time intervals. Data are from National Surveys on Drug Use and Health, 2004-2014 (n=14,457 newly incident cannabis users).

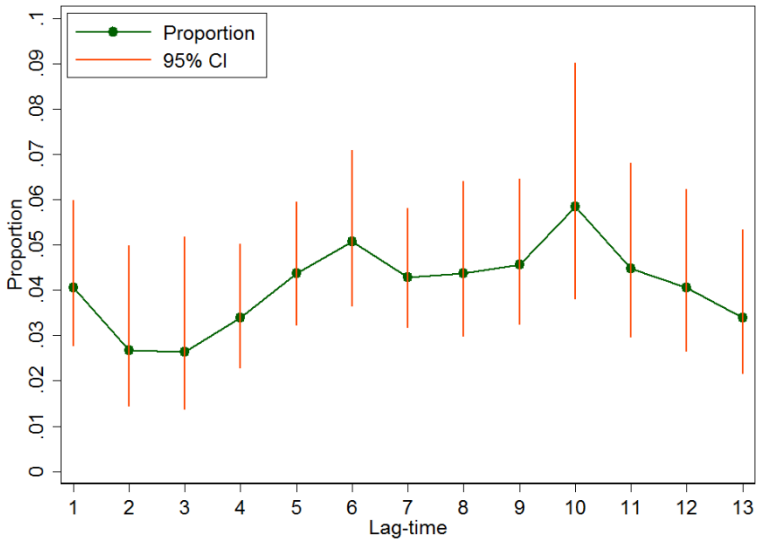


Figure C11. Meta-analytic summary proportion estimates of sedatives onset soon after cannabis onset over lag-time intervals. Data are from National Surveys on Drug Use and Health, 2004-2014 (n=14,457newly incident cannabis users).

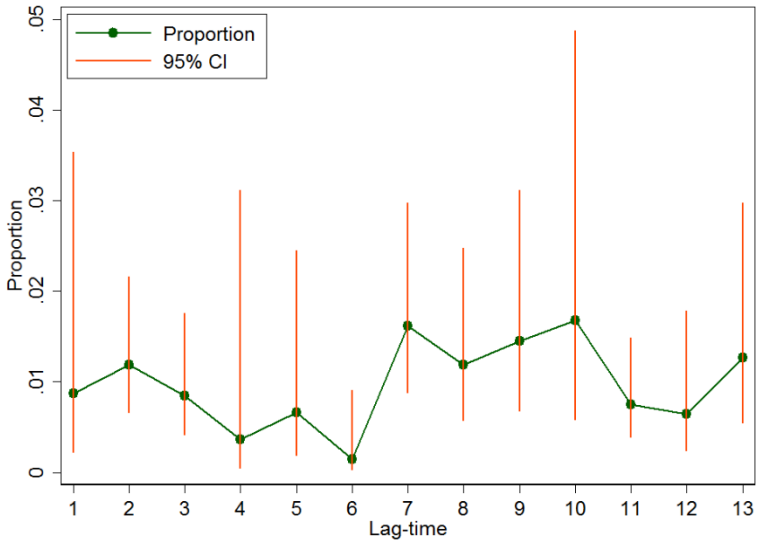


Figure C12. Meta-analytic summary proportion estimates of crack cocaine onset soon after cannabis onset over lag-time intervals. Data are from National Surveys on Drug Use and Health, 2004-2014 (n=14,457 newly incident cannabis users).

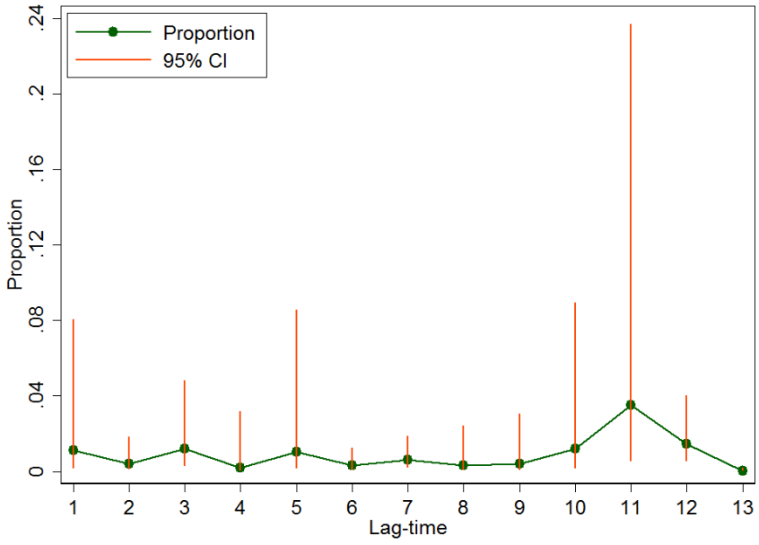


Figure C12. Meta-analytic summary proportion estimates of hallucinogens onset soon after cannabis onset over lag-time intervals. Data are from National Surveys on Drug Use and Health, 2004-2014 (n=14,457 newly incident cannabis users).

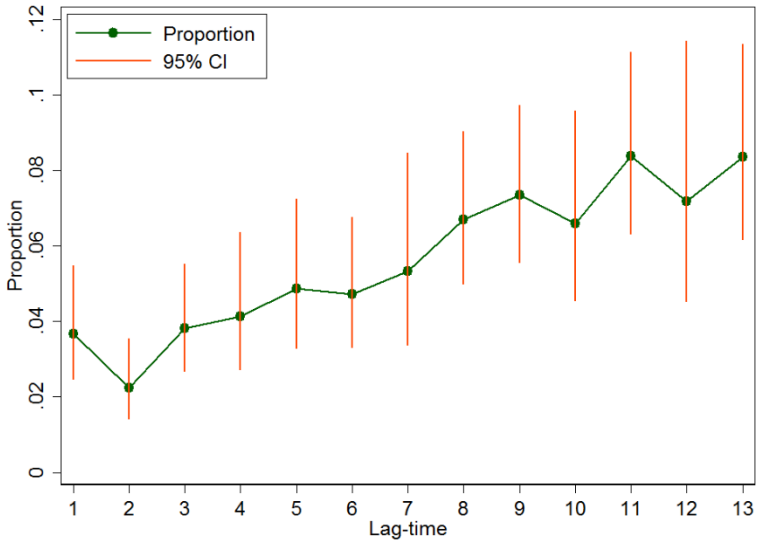


Figure C13. Meta-analytic summary proportion estimates of PCP onset soon after cannabis onset over lag-time intervals. Data are from National Surveys on Drug Use and Health, 2004-2014 (n=14,457 newly incident cannabis users).

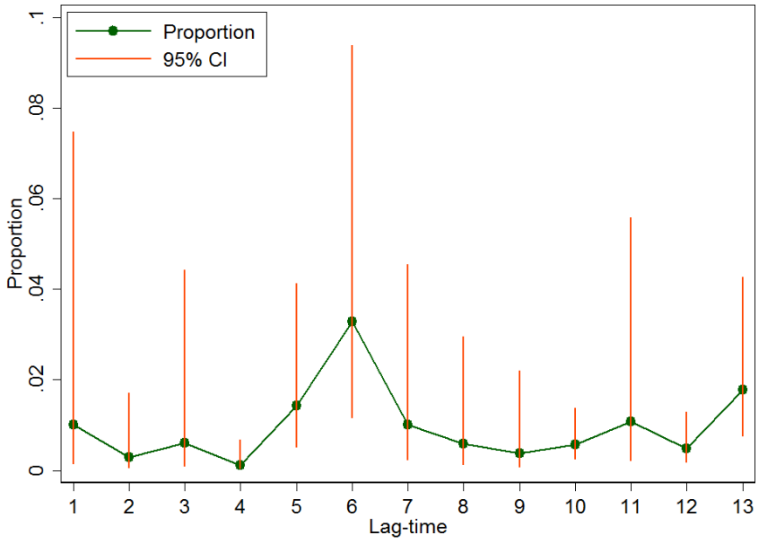


Figure C14. Meta-analytic summary proportion estimates of methamphetamine onset soon after cannabis onset over lag-time intervals. Data are from National Surveys on Drug Use and Health, 2004-2014 (n=14,457 newly incident cannabis users).

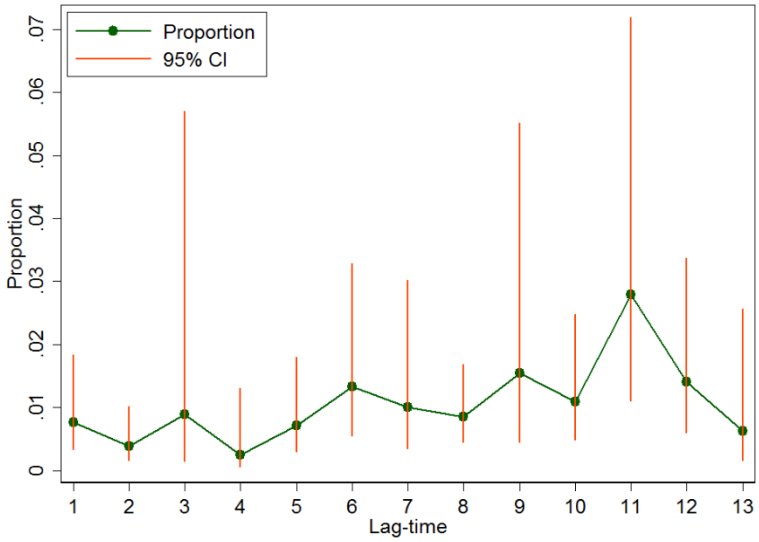


Figure C15. Meta-analytic summary proportion estimates of OxyContin onset soon after cannabis onset over lag-time intervals. Data are from National Surveys on Drug Use and Health, 2004-2014 (n=14,457 newly incident cannabis users).

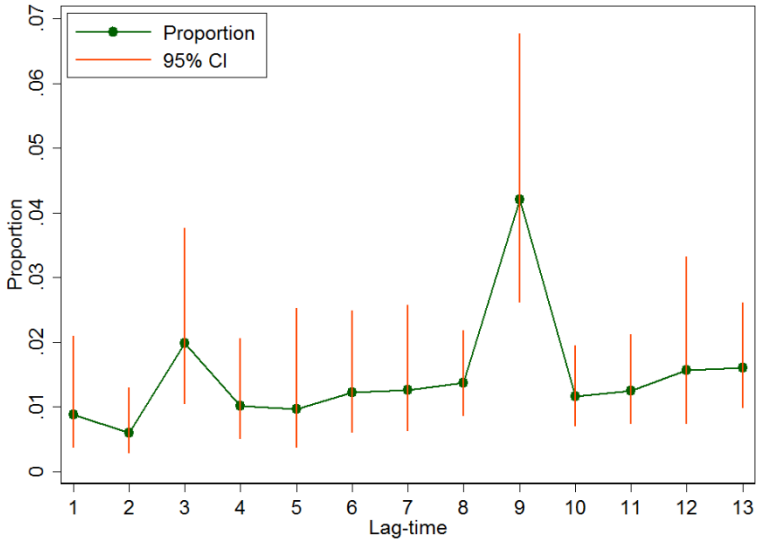


Figure C16. Meta-analytic summary proportion estimates of ecstasy onset soon after cannabis onset over lag-time intervals. Data are from National Surveys on Drug Use and Health, 2004-2014 (n=14,457newly incident cannabis users).

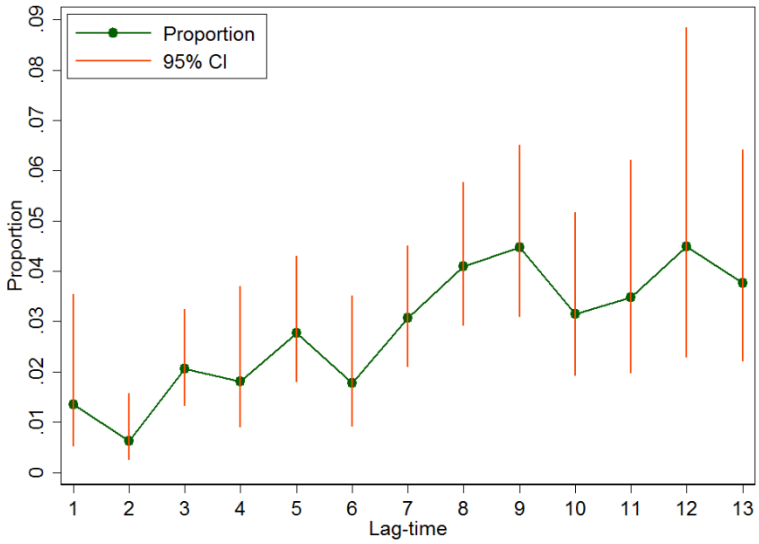


Figure C17. Meta-analytic summary proportion estimates of LSD onset soon after cannabis onset over lag-time intervals. Data are from National Surveys on Drug Use and Health, 2004-2014 (n=14,457newly incident cannabis users).

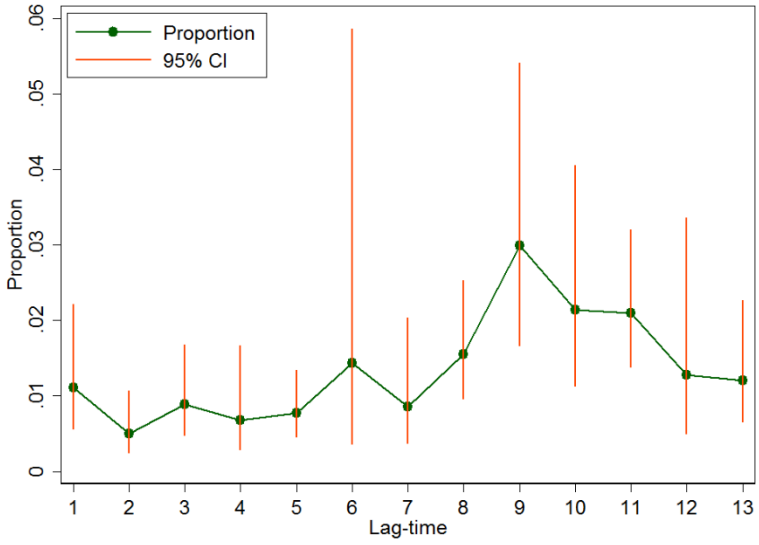


Figure C18. Meta-analytic summary proportion estimates of anxiolytics onset soon after cannabis onset over lag-time intervals. Data are from National Surveys on Drug Use and Health, 2004-2014 (n=14,457newly incident cannabis users).

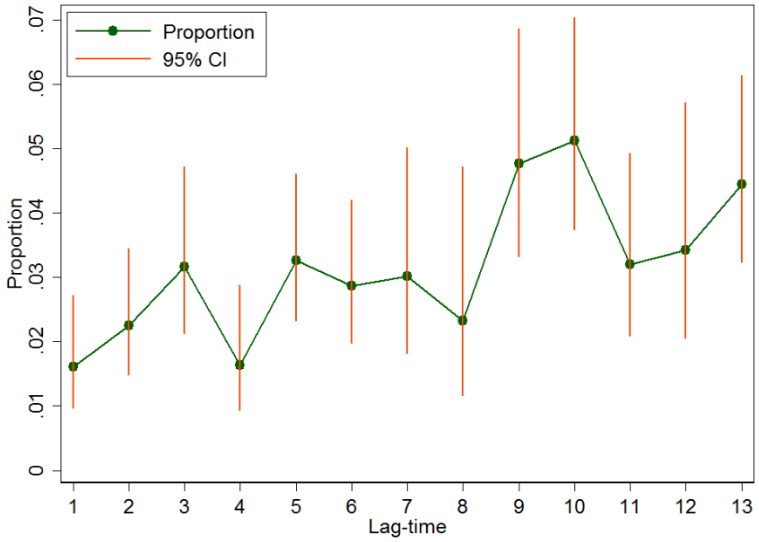


Figure C19. Meta-analytic summary proportion estimates of analgesics onset soon after cannabis onset over lag-time intervals. Data are from National Surveys on Drug Use and Health, 2004-2014 (n=14,457newly incident cannabis users).

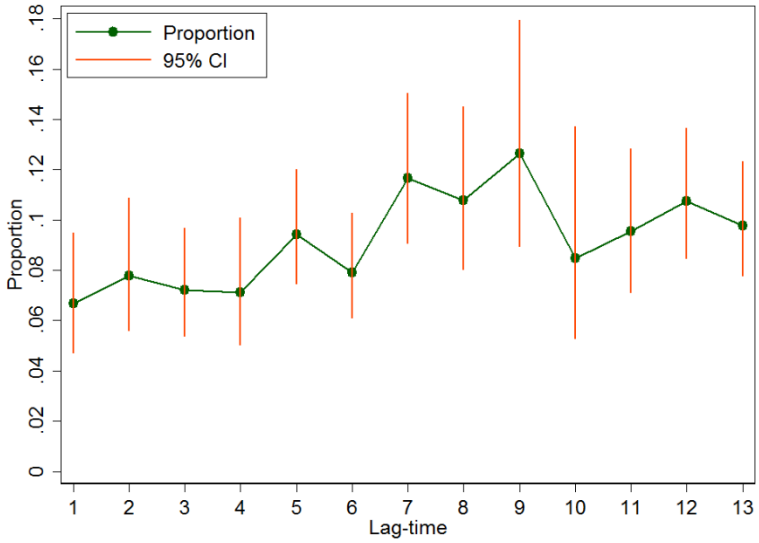
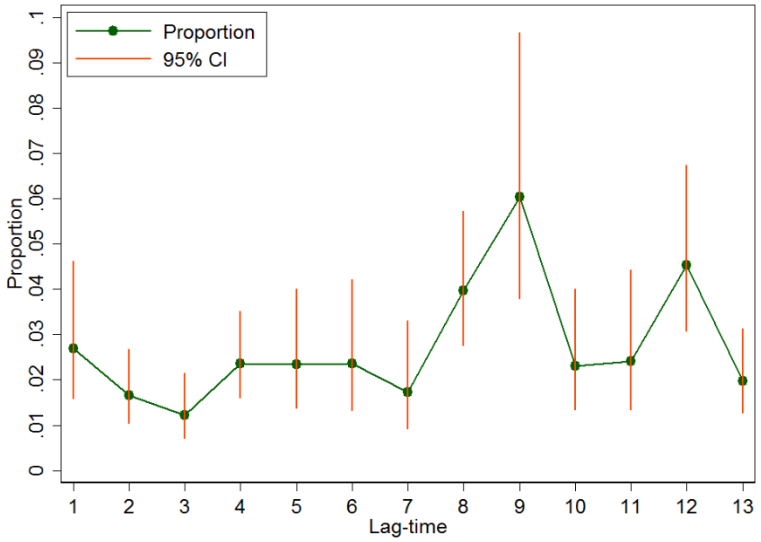


Figure C20. Meta-analytic summary proportion estimates of other stimulants onset soon after cannabis onset over lag-time intervals. Data are from National Surveys on Drug Use and Health, 2004-2014 (n=14,457 newly incident cannabis users).



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