# CONTRIBUTIONS TO THE EPIDEMIOLOGY AND MENTAL HEALTH CONSEQUENCES OF CANNABIS SMOKING

By

Brian John Fairman

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ABSTRACT

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Cannabis smoking might contribute to the incidence and course of major depression, but it is less clear whether this relationship is particularly pernicious when exposure occurs during adolescence. This hypothesis is guided by prior evidence that adolescence is a particularly vulnerable period of neurodevelopment, and early cannabis exposure may have a lasting toxic effect on normal emotional development. The first study in this dissertation research investigates the degree to which early-onset cannabis smoking (before age 18 years) might predict the later onset of a sustained spell of depressed mood in adulthood (herein, a 'depression spell'), as compared to never and later-onset cannabis users. The second study complements the findings therein and was motivated to inform on the extent to which depression spells were clinically relevant, with relevance operationally measured by functional impairment attributed to depression in an individual's occupational, social, and daily life. Data for these studies came from the U.S. National Surveys on Drug Use and Health (NSDUH), a program of annual cross-sectional surveys of large and nationally representative samples of community-dwelling U.S. residents aged 12 years or older.

The third and fourth studies of this dissertation sought to contribute to our understanding of the epidemiology of cannabis use disorders via two relatively novel and understudied patterns of cannabis smoking. In the first, the tobacco-cannabis combination called 'blunts', which has become an increasingly popular method of cannabis consumption in the U.S., was hypothesized to be associated with more cannabis problems (e.g., when blunt smokers are compared to their non-blunt cannabis smoking peers). Here also, the NSDUH epidemiological surveys made it possible to estimate the degree to which a history of blunt smoking is associated with the level of cannabis problems in a representative sample of recent

cannabis users. For the final study in this dissertation research, it was hypothesized that cannabis users who rapidly transitioned from the first drug opportunity to using cannabis might have a greater risk of later cannabis problems. Here, for this study, the data are from the collaborative WHO World Mental Health Surveys (WHO-WMHS), with cross-national data from 14 countries that made it possible to look beyond the boundaries of the U.S. for novel epidemiological evidence on cannabis smoking.

Results from these studies were informative. Early-onset cannabis smoking was associated with a later depression spell in adulthood: cases with an adult-onset depression spell were an estimated 70% more likely to have been exposed to using cannabis in adolescence, as compared to never users. However, the exposure odds ratio with respect to later-onset cannabis exposure was of similar magnitude, suggesting that early-onset cannabis exposure per se is less important than was hypothesized, and that the delay of cannabis onset until adulthood might not greatly affect the risk of a later depression spell. As for the issue of 'clinical relevance,' cases with recent depression spells suffered noteworthy functional impairment attributed to this mood disturbance, with greater impairment seen across at higher levels of cannabis problems. In specific, an estimated 25% (one in four) of the recent depression spell cases experienced severe to very severe functional impairment attributed to their depression. In the study of blunt smoking, as hypothesized, the level of cannabis problems was greater for blunt smokers and when there was more frequent recent blunt smoking, as compared to that experienced by cannabis users with little or no blunt smoking history. Findings from the cross-national epidemiological surveys were generally consistent with expectations -- namely, cannabis users who delayed their onset of cannabis smoking for a year or more after initially being offered the chance to try drugs were at a reduced chance of experiencing later cannabis-related problem outcomes.

This dissertation is dedicated to my family, friends, and loved ones who believed in and supported me.

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| | |
|---|---|
| 5HT | Serotonin |
| ACASI | Audio Computer-Assisted Self-Interviewing |
| AD | Alcohol Dependence |
| ADHD | Attention deficit hyperactivity disorder |
| AP | Alcohol Problems |
| APA | American Psychiatric Association |
| ATS | Amphetamine-type stimulants |
| CAI | Computer Assisted Interviewing |
| CAPI | Computer-Assisted Personal Interviewing |
| CBSA | Census core-based statistical areas |
| CBT | Cognitive Behavioral Treatment |
| CD | Cannabis Dependence |
| CFA | Confirmatory Factor Analysis |
| CFI | Comparative fit index |
| CI | Confidence Interval |
| CIDI | Composite International Diagnostic Interview |
| CM | Contingency Management |
| CP | Cannabis Problems |
| CUD | Cannabis Use Disorder |
| DALY | Disability Adjusted Life Years |
| DEPEND | Dependence |
| df | Degrees of Freedom |

| | |
|---|---|
| DHHS | Department of Health and Human Services |
| DR | Designated Respondent |
| DSM | Diagnostic and Statistical Manual |
| DTC | Delayed Treatment Control |
| DU | Dwelling Unit |
| ECA | Epidemiologic Catchment Area |
| EFA | Exploratory Factor Analysis |
| EOCU | Early-Onset Cannabis Use |
| EV | Eigenvalues |
| FI | Field Interviewer |
| FTND | Fagerstrom Test of Nicotine Dependence |
| GWAS | Genome-Wide Association Study |
| HARM | Harmful Socially Maladaptive or Hazardous |
| HR | Hazard Ratio |
| ICD | International Classification of Diseases |
| IMPAIR | Functional Impairment |
| IRB | Institutional Review Board |
| IRD | Internationally Regulated Drug |
| MAU | Maladaptive Alcohol Use |
| MCU | Maladaptive Cannabis Use |
| MDD | Major Depressive Disorder |
| MDE | Major Depressive Episode |
| MET | Motivational Enhancement Treatment |

| | |
|---|---|
| MI | Modification Indices |
| MTF | Monitoring the Future |
| NA | Noradrenaline |
| NCS | National Comorbidity Study |
| NCS-R | National Comorbidity Study – Replicate |
| NDSS | Nicotine Dependence Syndrome Scale |
| NHSDA | National Household Survey on Drug Abuse |
| NIDA | National Institute of Drug Abuse |
| NLAES | National Longitudinal Alcohol Epidemiologic Survey |
| NSDUH | National Surveys on Drug Use and Health |
| OR | Odds Ratio |
| PSU | Primary Sampling Unit |
| RMSEA | Root Mean Error of Approximation |
| RR | Relative Risk |
| SAMHSA | Substance Abuse and Mental Health Services Administration |
| SAOC | Subject-As-Own-Control |
| SDS | Sheehan Disability Scale |
| SMR | Standardize mortality ratio |
| SNP | Single nucleotide polymorphisms |
| SSR | State Sampling Region |
| SSU | Secondary Sampling Unit |
| TCO | Time to Cannabis Onset |
| TD | Tobacco Dependence |

| | |
|---|---|
| THC | Delta-9-tetrahydrocannabinol |
| TLI | Tucker-Lewis Index |
| UNODC | United Nations Office of Drug and Crime |
| WHO | World Health Organization |
| WMHS | World Mental Health Survey |
| Wt | Weighted |
| YRBS | Youth Risk Behavioral Surveillance |

# CHAPTER 1. AIMS AND OBJECTIVES

> Hashish has nothing of that ignoble drunkenness about it which the races of the North obtain from wine and alcohol; it offers an intellectual intoxication.
>
> (Theophile Gautier, 1884, as quoted in Bey & Zug, 2004, p. 417)

This dissertation was conceived around a different sort of 'intellectual intoxication' - that of answering a series of research questions pertaining to the patterns of cannabis smoking that might lead to problematic use or depressive mood states.

## 1.1. Study 1. Are Early-Onset Cannabis Users At An Increased Risk Of Depression Spells?

Of important public health concern is whether depression is elevated as a result of youthful cannabis involvement (C. Y. Chen, Wagner, & Anthony, 2002; Fergusson & Horwood, 1997; Grant, 1995; B. E. Green & Ritter, 2000). If so, one implication may be that delaying cannabis onset until adulthood might reduce the risk of later depression. Thus, the hypothesis of this research focused on whether the first experience of a sustained spell of depressed mood, with allied psychosomatic features (herein a "depression spell") might be predicted by a potentially toxic exposure earlier in life -- i.e., early-onset cannabis smoking. The aim of this research can be summarized as follows:

> **AIM 1.** Estimate the degree to which early-onset (onset $\leq$ 17 years) and adult-onset (18+ years) cannabis smoking are associated with a post-exposure first onset of a depression spell in adulthood, within a conceptual model that accounts for time-invariant characteristics of sex, age, and race/ethnicity, and variation in tobacco and alcohol use.

### 1.2. Study 2. Does the Level of Cannabis Problems Predict the Level of Functional Impairment Attributed to Recently Active Depression?

Depression causes not only mental suffering, but can also interfere with the individual's ability to carry out everyday tasks, go to work, and engage in meaningful relationships. Little is known about the degree to which these functional impairments attributed to depression are associated with cannabis smoking. Further, some readers may question the clinical relevance or significance of the depression spell concept under study. Therefore, Study 2 proposes to do the following:

> **AIM 2.** Clarify levels of functional impairment attributed to the depression spell under study, and estimate the degree to which the level of cannabis problems is associated with the functional impairment attributed to depression in recently active cases, while accounting for differences in background characteristics, tobacco and alcohol use, and other relevant covariates.

### 1.3. Study 3: Do Cannabis Smokers with a History of 'Blunt' Smoking Differ in the Experience and Degree of Cannabis Problems?

The practice of cannabis 'blunt' smoking (i.e., combining cannabis within a tobacco cigar shell) has gained popularity in the U.S. since the 1990s (Golub, Johnson, & Dunlap, 2005; Timberlake, 2013). Pre-clinical and clinical findings motivate a concern over a functional interaction between tobacco and cannabis (Agrawal et al., 2009; Castañé et al., 2002; Valjent, Mitchell, Besson, Caboche, & Maldonado, 2002; Vandrey, Budney, Hughes, & Liguori, 2008). However, it is unclear whether blunt smokers have a higher level of cannabis problems than their non-blunt cannabis smoking counterparts (Ream, Johnson, Sifaneck, & Dunlap, 2006; Timberlake, 2013). The main aim of Study 3 was to produce the following evidence:

**AIM 3.** Estimate the degree to which a history of cannabis 'blunt' smoking is associated with the level of cannabis problems experienced, within a conceptual model adjusting for the influence of sex, age, race/ethnicity, and other potential time-invariant covariates.

### 1.4. Study 4: Does Delaying Onset of Cannabis Smoking After Onset of First Opportunity Account for Variations in Risk for Later Cannabis Problems?

As already mentioned, early-onset cannabis smoking is a marker for later problematic use. Previous studies have measured this time to cannabis onset in relation to time since birth. However, not everyone has an equal probability of being offered a chance to try cannabis, and may be offered this first opportunity at different ages (Van Etten & Anthony, 1999; Van Etten, Neumark, & Anthony, 1997; Wagner & Anthony, 2002b). Further, individuals may vary to the degree they use cannabis soon after being presented a chance to try it. This source of variation has not typically been accounted for or studied in relation to the later risk of experiencing cannabis problems. Study 4 seeks to understand the relationship between time to cannabis onset, measured as the number of years from the first chance to try drugs until first cannabis onset, and the subsequent post-exposure risk of later cannabis problems. The main aim is summarized as follows:

**AIM 4.** Estimate the degree to which delaying cannabis onset after the first chance to try drugs might account for later levels of cannabis problems among a cross-national sample of adults whose only internationally regulated drug (IRD) use has involved cannabis (i.e., 'cannabis only' users).

# CHAPTER 2. BACKGROUND AND SIGNIFICANCE

> With hashish, the affective faculties reach the same degree of overexcitement as do the intellectual faculties. The emotions have the mobility and, at the same time, the "tyranny of ideas." The individual uses the power to resist his violent feelings until finally the mind itself reaches the point of incoherence.
>
> (Moreau, 1845, p. 64)

The purpose of this chapter is to provide the reader with a scholarly and relevant background on the topics pertaining to this dissertation research. As such, a part of the background focuses on general related topics of the history, biology, and epidemiology of cannabis smoking, but in addition, specific attention is paid to depression, functional impairment, and blunt smoking, since each topic features prominently in this research on cannabis.

## 2.1. Cultivation and Common Preparations of Cannabis

There are three varieties of cannabis plant, each containing variable amounts of what is regarded as the primary psychoactive drug compound in this plant, which is known as delta-9-tetrahydrocannabinol (THC). The three varieties, *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis,* are native to Asia, but have now spread throughout the world (Hart, Ksir, & Ray, 2009). *C. sativa* is the most common variety associated with use of cannabis as a drug. This plant can grow up to 20 feet tall, and can thrive under a wide variety of temperature, soil, sunlight, and moisture conditions, which promotes production of cannabis as local or regional enterprise rather than requiring international trafficking, such as for cocaine or heroin (Gold, 1991; United Nations Office on Drugs and Crime, 2011). Cannabis is primarily cultivated for its

psychoactive properties, but its fiber (called hemp) has historical uses as in manufacture of clothing and rope (Abel, 1980; Gold, 1991). Cannabis is dioecious, meaning it has separate male and female plants (Gold, 1991). Female cannabis plants produce a resin, which coats the flowering tops and leaves of the plant, and this resin protects the plant from moisture loss (Gold, 1991). The psychoactive properties of cannabis is concentrated in the resin, and the parts of the cannabis plant containing more resin are the most potent (Hart et al., 2009). Humans cultivating cannabis as a drug breed sub-variations of *C. sativa* to produce more resin, or often growing it under environmental conditions thought to maximize potency (Abel, 1980; Hart et al., 2009).

The cannabis plant is processed into different drug preparations that vary in potency related to the concentration of cannabis resin contained therein. Historically, the most potent preparation of cannabis has been called *hashish*, or the extract 'hashish oil' described below, which is the cannabis resin compressed into blocks or cakes (Gold, 1991). Hashish comes in various levels of purity, depending on the process of separating the resin from the rest of the plant matter (Hart et al., 2009). Hashish oil is highly purified resin, dissolved in organic solvents, and may be added to herbal cannabis in order to increase potency (Gold, 1991; Hart et al., 2009). Less potent herbal cannabis, commonly referred to the slang term *marijuana* (or *marihuana*), is composed of the dried and crushed remnants of the leaves and flowering tops of the cannabis plant (Gold, 1991; Hart et al., 2009). In India, which has a long history of cannabis use in its culture, has three common preparations, *bhang*, which is a dried powder made from cannabis leaves and mixed into drinks (least potent), *ganja*, which is made from the flowers and upper leaves, and *charas*, which is pure resin (similar to hashish) prepared from the flowers at the height of bloom (Abel, 1980; Hart et al., 2009).

The most recently introduced cannabis preparation is known as 'dabs,' apparently akin to 'hashish oil,' but not yet well-characterized. The term ‘dabbing’ originates from an American colloquial phrase of a ‘little dab will do ya’, meaning a small amount will go a long way. The phrase originated in the 1950s from the marketing campaign for Brylcreem, a men’s hair styling product (“Brylcreem,” 2014). In the context of a cannabis preparation, a ‘dab’ refers to the smoking of a small amount of hash oil, particularly butane hash oil (BHO), which has a high THC concentration (Black, 2012). Butane is used as a chemical solvent to extract THC from plant matter, with the subsequent step of heating the butane/THC mixture to evaporate the butane. Since butane is highly combustible, producing BHO can be very dangerous. It is claimed that the THC content of dabs is greater than the THC content of prior cannabis extract preparations, and that risk of THC overdose has become a possibility with the 'dabs' formulation of cannabis products (C. Roberts, 2013). Initial field survey research on users of dabs in Humboldt County, California, is underway and a NIDA research project proposal currently is under review (James Anthony, personal communication, 2014). As of April 2014, a bibliographic search of the scientific and public health literature disclosed no published journal articles on 'dabs'. For example, the return from a NIH National Library of Medicine PubMed search for 'dabs & cannabis’ was "No items found" and the PubMed return for 'dabs THC' was "Your search for dabs THC retrieved no results."

### 2.2. Cannabis History and Beginnings of Public Health and Moral Concerns

Humans have been cultivating cannabis for thousands of years, and have used cannabis for a variety of purposes than simply an intoxicant. Cannabis has been variously used to make rope and clothing, as livestock feed (as seed), as medicine, and for religious purposes (Gold,

1991). Across this long time period, humans have debated the physical, psychological, and ethical consequences of cannabis smoking, which have been shaped by myths, legends, literature, religion, propaganda, and governments. Covering these historical, social, and legal issues of cannabis use is important as background for our understanding of the context of the public health and scientific issues surrounding the study of cannabis.

Humans have cultivated cannabis for the use as hemp dating back at least 10,000 to the Stone Age (Abel, 1980). It is unclear whether cannabis' intoxicating properties were known to pre-history. According to historians, the first references to cannabis being consumed appear in the Chinese pharmacopeia, the *Pen Ts'ao*, compiled by Emperor Shen-Nung in 2737 B.C. Among cannabis' listed uses were for relief of these ailments: "female weakness (menstrual fatigue), gout, rheumatism, malaria, beri-beri, constipation, and absentmindedness" (Abel, 1980; Walton, 1938). Cannabis was well known to other cultures of antiquity, including having prominent religious significance in the holy Indian *Vedas* (at least 2000 B.C.), trade as hemp among ancient Greeks ($4^{th}$ century B.C.), and referenced by the Romans in the influential *materia medica* published by Dioscorides in 70 A.D. (Abel, 1980). Among Arabic cultures, hashish was probably known to them by the tenth century A.D. (Abel, 1980). One of the more infamous legends about cannabis involved the merchant and traveler Marco Polo. Taken prisoner in Italy around 1297 A.D., Polo recounted the tale of a ruthless Persian ruler Hasan-ibn-Sabah "Old Man of the Mountains", who used his religiously fanatic cult to terrorize and conduct politically motivated murders (Abel, 1980). While Polo did not directly implicate hashish, Hasan's followers became known variously as Heyssessini, Assinini, Hashshashin, or Hashishiyya, and were associated with the use of hashish. This is reportedly where the word "assassin" originates (Abel, 1980; Hart et al., 2009; Roffman, Schwartz, & Stephens, 2006).

By the 18th and 19th centuries, the properties of cannabis intoxication came to the attention of Western cultures through colonial expansion and the travels of scientific or literary figures. In 1798, Napoleon invaded Egypt and soldiers stationed there were introduced to hashish, which helped infuse French curiosity when they returned with tales of the drug (Abel, 1980). One of the first to study cannabis scientifically was Dr. Jacques-Joseph Moreau (1804-84). His interest was in the potential for cannabis to produce symptoms similar to insanity without first suffering mental illness. His study of hashish (in which he recounts his own and other's experiences with hashish) was published in *Hashish and Mental Illness* (1845). It describes many of the effects of cannabis we know today such as euphoria, distortion of space and time, and hallucinations or illusions (Abel, 1980; Moreau, 1845). Among the effects of hashish intoxication Moreau discusses were disturbances of emotions:

> One day in the middle of a very intense hashish intoxication, my ears were suddenly struck by the sound of bells. This was hardly an hallucination but, being in a sad mood, I interpreted this sound, which I would not normally have been aware, as the tolling of a funeral bell. (Moreau, 1845, pp. 64–65)

Moreau's work greatly influenced French Romanticist Pierre Jules Theophile Gautier, who established the Hashish Club in Paris, and which included literary luminaries such as Alexandre Dumas, Gerard de Nerval, Victor Hugo, Ferdinand Boissard, and Eugene Delacroix (Abel, 1980; Gold, 1991; Roffman et al., 2006).

Notwithstanding the fascination for cannabis and hashish among select circles, it remained an obscure drug to Western cultures, and governments generally showed little interest in cannabis control before the 20th century, except to encourage its cultivation and sometimes to raise taxes from its cultivation or sale. Concern over the 'vices' caused by alcohol and opium

were more salient, however, this would soon change. Cannabis was widely used in British-controlled India, and in the mid-19th century there was growing concern over the "cannabis problem". This led to the formation of a commission to study the cultivation, preparation, and physiological, psychological, and moral effects of cannabis in the population (Abel, 1980). Ganja consumption among the lower classes was blamed for everything from ailing health, insanity, and violent crimes (Abel, 1980). Proponents of cannabis prohibition were weighed against the strong economic interests of British taxation related to cannabis production. Based upon written and oral testimony of 1,193 witnesses, most of who had little direct expertise with cannabis or relied on dogmatic opinions, the Committee concluded that moderate use had little physical dangers, although excessive use could lead to 'insanity' in predisposed individuals, and cannabis had no significant adverse moral influences (Abel, 1980). Their recommendation was for continued taxation. Despite methodological flaws noted elsewhere, the Indian Hemp Drugs Report of 1893-94 was the most comprehensive study on cannabis at the time.

In the United States, public concerns over cannabis consumption grew during the early 20th century due to increased propaganda, sensationalized media reports, and misleading statements from government officials responsible for drug control. There was a racial/xenophobic component to the acceptance and perpetuation of these concerns over cannabis, which was associated with African-American Southern Blacks, Chinese immigrants, and Mexicans living along the U.S. border (Hart et al., 2009). Though scant empirical evidence was proffered, public officials like the U.S. Commissioner of Narcotics, Harry Anslinger, hyped the dangers of cannabis use as being responsible for violence, crime, and sexual perversion. This paranoia inevitably led to the Marijuana Tax Act of 1937, which taxed every level of cannabis production, distribution, sale, and use, and along with state laws prohibiting cannabis possession

or use, effectively made use of cannabis illegal (Hart et al., 2009). Later government reports in the U.S. and elsewhere found little empirical support for the myths surrounding the dangers of cannabis, and despite the Marijuana Tax Act being overturned by the U.S. Supreme Court in 1969, cannabis remains a Schedule I substance (hence illegal) under the Controlled Substances Act (CSA) of 1970. Nevertheless, the pendulum has been swinging back over the past 20 years as more U.S. States have allowed cannabis for medicinal uses, and as of January 2014 two states (Washington and Colorado) had passed laws allowing the legal consumption of cannabis for recreational purposes.

### 2.3. The Pharmacology of Cannabinoids

The pharmacology of cannabis is important for understanding the possible biological and neurological mechanisms as might account for adverse mental health consequences of cannabis smoking. Cannabis is not a single drug, but is a mixture of over 400 compounds, with at least 60 identified as cannabinoids (Ashton, 2001). Among these, as noted in Section 2.1, the main psychoactive constituent of cannabis is delta-9-tetrahydrocannabinol (see Figure 2.3.1; abbreviated Δ-9-THC, or simply THC). THC is found in the plant's resin and in the leaves, flowers, and seeds, with higher concentrations of THC in the resin and flowers. Prior reports have claimed that the THC content of herbal cannabis has increased over the decades since 1960, with some estimates of a 10-30 fold increase; however, others contend a much more modest two-fold change (Ashton, 2001; Hall & Swift, 2007; Mehmedic et al., 2010). In government confiscated samples, THC content of herbal cannabis ranges between 3-5% (Mehmedic et al., 2010).

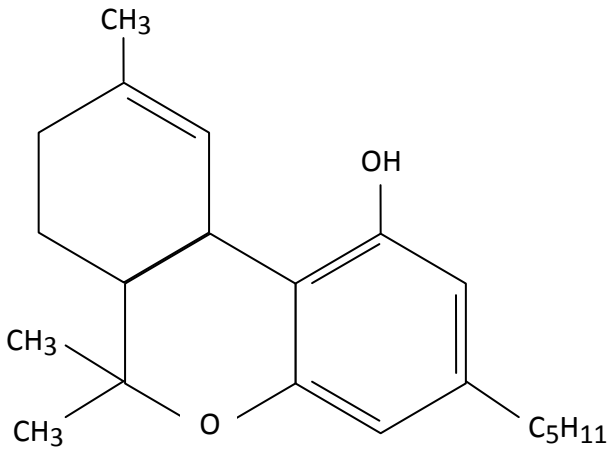



**Figure 2.3.1.** Chemical structure of delta-9-tetrahydrocannabinol

There have been no reported cases of fatal overdose on cannabis *per se*; the likely quantify for a fatal human dose greatly exceeds the amount of even a typical heavy cannabis user (Hall & Degenhardt, 2009). According to media and online reports, there have been instances of non-lethal 'overdose' (as defined loosely as inadvertent consumption of many times more than the effective dose of hash oil, dabs, or other high THC concentration products), although the possibility of fatal overdose remains uncertain (C. Roberts, 2013).

Cannabis can be smoked or ingested, and there are several methods of delivery. The main route of THC administration is by inhalation of smoke from combusted herbal cannabis. Herbal cannabis can be smoked by rolling dried plant matter into cigarette paper (the resulting product is called a ‘joint’), or smoked directly from a pipe or water pipe (a.k.a. a ‘bong’, or a device that uses water to humidify the smoke for easier and deeper inhalation; Gold, 1991). Tobacco cigars can also be used as a cannabis delivery device, where some of the tobacco contents are removed and replaced with cannabis, then smoked. This practice is called ‘blunting’, and the resultant cigar-cannabis combination is called a ‘blunt’. A more modern high-tech practice is to use a specialized device to vaporize, rather than burn cannabis, thereby reducing the carcinogenic

byproducts and irritating effects of inhaling cannabis smoke. Cannabis is fat and alcohol soluble, and can be ingested through foods and liquids, as is the case with South Asian 'bhang,' often prepared by mixing plant material in drinks and candies (Ashton, 2001; Gold, 1991; Hart et al., 2009).

The mechanisms of THC absorption, metabolism, and excretion greatly affect the circulating blood concentration of THC. Via inhalation, THC is more rapidly absorbed into the blood and distributed to the brain (Hart et al., 2009). About 50% of the THC in cannabis smoke is absorbed by the lungs with inhalation (Ashton, 2001). Physiological and psychological effects are often felt within minutes, and can last for an average of two hours depending on dose (Ashton, 2001; Hart et al., 2009). Because THC is lipophilic, it can be stored in the fatty tissues, and then released slowly in the blood stream (Ashton, 2001; Hart et al., 2009). Cannabis ingested in food or drink produces around 25-30% lower THC blood concentration than smoking due to the first pass effect of the liver (Ashton, 2001). The slower absorption delays onset of THC effects, but also can produce more prolonged and steady intoxication (Ashton, 2001). THC is metabolized by the liver into at least 45 metabolites, of which 11-hydroxy-delta-9-THC is a major metabolite (Ashton, 2001; Hart et al., 2009). Some metabolites are psychoactive and may be more potent than THC itself (Ashton, 2001). THC has a half-life of about 19 hours, and complete elimination may take up to 30 days (Ashton, 2001; Hart et al., 2009). Excretion occurs primarily through the gut, which allows for reabsorbed of THC and THC metabolites, but a smaller portion is eliminated in the urine (Ashton, 2001; Hart et al., 2009). As a result of uptake into fatty tissue and reabsorption by the gut, there is no clear correlation between blood or urine THC-metabolite concentration and level of intoxication (Ashton, 2001).

Since THC was first isolated by Gaoni and Mechoulam (1964), there have been a number of advances in the pharmacodynamics of cannabinoids on the human brain. Devane and colleagues (1988) were the first to identify binding sites for cannabinoids in rat brains, which today are labeled CB1 receptors. Subsequent work in pig models by Devane and others (1992) discovered the first endocannabinoid, called anandamide (meaning "bliss" in Sanskrit). A second type of cannabinoid receptor (CB2) was then identified and appears to play a role in cellular mechanisms of immune response (Munro, Thomas, & Abu-Shaar, 1993). CB1 receptors have been found throughout the human body, but within the brain there are greater densities in the basal ganglia, cerebellum, hippocampus, thalamus, cerebral cortex, and the nucleus accumbens (Hart et al., 2009; Herkenham et al., 1991). THC, along with other drugs such as opioids, cocaine, amphetamines, and nicotine, activate the release of dopamine in the nucleus accumbens, activating reward systems in brain (Ashton, 2001).

### 2.4. The Diagnosis of Cannabis Use Disorders

Whether termed drug *addiction*, *habituation*, or *dependence*, there comes a point in the lives of some drug users when their drug-using behavior can be described as 'pathological' or 'compulsive', but some scholars voice objections to this 'medicalizing' of cannabis problems. Nonetheless, differentiating between pathological and non-pathological patterns of drug use can have important implications for clinical treatment, public health prevention strategies, and scientific research. The concept of a *syndrome* is employed to characterize pathological drug use where symptoms may encompass physical, mental, and behavioral manifestations, and where no specific set of symptoms are necessary and sufficient. In this regard, a syndrome is considered to be "a cluster of symptoms that co-occur in a way that signals the presence of an underlying

disorder" (Babor, 2006). Characteristics of a drug *dependence* syndrome include disturbances of the mental life, disturbances of behavior, and neuroadaptive changes (Anthony, 2006; Edwards, Arif, & Hodgson, 1981). Allied with the concept of a drug dependence syndrome has been the recognition that problematic drug use may be manifested by socially maladaptive or hazard-laden consequences, such as interference with important social roles or occurring under physically hazardous situations (Edwards et al., 1981). This type of maladaptation has been often termed as drug *misuse* or *abuse*. In this dissertation, drug abuse is only referred to as such when specifically referencing the construct as defined in the DSM. Otherwise, these problems are collectively referred to as maladaptive cannabis or alcohol use (MCU or MAU), depending on which drug is being referenced.

The diagnosis of cannabis dependence follows along similar lines as that of other drugs such as alcohol, opioids, and cocaine. Two similar and converging classification systems of cannabis dependence come from the World Health Organization (WHO) and the American Psychiatric Association (APA). The WHO's nomenclature is detailed in the *International Classification of Diseases, 10$^{th}$ revision* (ICD-10), while the APA's comes from its *Diagnostic and Statistical Manuals* (e.g., DSM-IV, DSM-5). Drug dependence clinical criteria from ICD-10 and DSM-IV are listed in Table 2.4.1. Although most criteria for dependence are common across substances, the DSM-IV excluded cannabis withdrawal as clinically insignificant (American Psychiatric Association, 1994). This conclusion has been challenged by more recent epidemiologic studies (Budney, Hughes, Moore, & Vandrey, 2004). Diagnosis of cannabis dependence under ICD and DSM-IV requires presence of three or more features in the same 12-month period. With respect to the clinical features of socially maladaptive or hazardous cannabis use (DSM "abuse"), these features are listed in Table 2.4.2.

During the writing of this dissertation, a new DSM was published (DSM-V; American Psychiatric Association, 2013), with important changes in diagnostic criteria. First, there is no longer a distinction between concepts of dependence and abuse; both are subsumed under a single set of diagnostic criteria called 'cannabis use disorder'. Second, whereas DSM-IV cannabis dependence required three or more co-occurring clinical features, DSM-5 requires only two. Third, a feature of "craving, or a strong desire or urge to use cannabis" was added to the list of features. Fourth, arrest or legal problems due to or the result of cannabis intoxication is no longer considered part of the clinical features.

**Table 2.4.1.** Clinical Features and Criteria for Cannabis Dependence from the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) and the *WHO International Classification of Diseases, 10th Revision* (ICD-10).

| **DSM-IV** |
|---|
| Dependence or significant impairment or distress, as manifested by 3 or more of the following during a 12 month period:<br>1. Tolerance, as defined by either a need for markedly increased amounts of cannabis to achieve intoxication or desired effect, or markedly diminished effect with continued use of the same amount of cannabis<br>2. Cannabis is often taken in larger amounts or over a longer period than was intended<br>3. There is a persistent desire or unsuccessful efforts to cut down or control cannabis use<br>4. A great deal of time is spent in activities necessary to obtain cannabis (e.g., driving long distances), use cannabis (e.g., socializing with cannabis using friends), or recover from its effects<br>5. Important social, occupational, or recreational activities are given up or reduced because of substance use<br>6. Cannabis use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by cannabis (e.g., chronic cough related to smoking; excessive sedation resulting from repeated use of high doses) |

**Table 2.4.1.** (Cont'd)

| **ICD-10** |
|---|
| Three or more of the following manifestations should have occurred together for at least 1 month or, if persisting for periods of less than 1 month, should have occurred together repeatedly within a 12-month period:<br>1. A strong desire or sense of compulsion to use cannabis<br>2. Difficulties in controlling cannabis-taking behavior in terms of its onset, termination, or levels of use<br>3. A physiological withdrawal state when cannabis use has ceased or been reduced, as evidenced by: a characteristic withdrawal syndrome for the substance; or use of the same (or closely related) substance with the intention of relieving or avoiding withdrawal symptoms<br>4. Evidence of tolerance, such that increased doses of cannabis are required in order to achieve effects originally produced by lower doses<br>5. Progressive neglect of alternative pleasures or interests because of cannabis use, increased amount of time necessary to obtain or use cannabis or to recover from its effects<br>6. Persisting with cannabis use despite clear evidence of overtly harmful consequences, such as depressive mood states consequent to periods of heavy use, or cannabis-related impairment of cognitive functioning; efforts should be made to determine that the user was actually, or could be expected to be, aware of the nature and extent of the harm. |

**Table 2.4.2.** Features of Socially Maladaptive or Hazardous Cannabis Use.

| **Features** |
|---|
| 1. Cannabis used frequently interfered with work or responsibilities at school, on a job, or at home.<br>2. Cannabis caused arguments or other serious or repeated problems with your family, friends, neighbors, or co-workers AND continued to use despite these problems.<br>3. Used cannabis in situations where one could get hurt, for example when riding a bicycle, driving, operating a machine, or anything else.<br>4. Arrested or stopped by the police because of driving under the influence of cannabis or because of one's behavior due to being [high/drunk]. |

## 2.5. The Epidemiology of Cannabis Smoking

The following sections describe the epidemiology of cannabis smoking. This information is organized around five rubrics that encapsulate five broad questions the field of epidemiology seeks to hold a lens to concerning the understanding of diseases or adverse health conditions (Anthony & Van Etten, 1998): 1) Quantity - How many are affected?; 2) Location – Where are affected cases more likely to be found?; 3) Causes – Why do some people become cases while others do not?; 4) Mechanisms – What processes link who becomes a case and continues to remain a case?; 5) Prevention and control – What can be done to prevent or intervene in the disease process?

### 2.5.1. Quantity and Location

Cannabis is more widely used around the world than any other internationally regulated drug (IRD). An estimated 3% to 5% of the global population 15 to 64 years of age use cannabis annually, representing roughly 119 to 224 million people (Figure 2.5.1) (United Nations Office on Drugs and Crime, 2012). By comparison, fewer people use cocaine, opiates/opioids, amphetamine-type stimulants (ATS), and ecstasy combined. Cannabis is more prevalent in established market economies, such as the United States, the European Union, Canada, and Australia (Figure 2.5.2). Lower estimates in less economically developed regions such as Africa (5-13%) and Asia (1-3%) may be due to a lack of high-quality data (United Nations Office on Drugs and Crime, 2012). Nevertheless, these regions represent a large proportion of the world's population, and even low estimates could translate into a substantial number of cannabis users.

Cross-national estimates of cannabis use are also available via the World Health Organization World Mental Health Survey Initiative (WHO-WMHSI). These surveys estimate

the highest lifetime cumulative incidence for cannabis smoking occurs in the U.S. (42%) and New Zealand (42%), moderate sizes (10-20%) in countries such as Colombia, Belgium, France, Germany, Netherlands, Spain, and Israel, and the lowest estimates (<10%) in Mexico, Italy, Ukraine, Lebanon, Nigeria, South Africa, Japan, and the People's Republic of China (Degenhardt et al., 2008).

Few studies are available to estimate the prevalence of cannabis smoking in India, despite its historical tradition of cannabis use in its culture, significant production of cannabis and resin, and large population. Previously published reports from the United Nations Office of Drug and Crime (UNODC) estimate the prevalence of cannabis in India to be around 3.2% as of 2000 (United Nations Office on Drugs, 2006). More recent studies report prevalence estimates as high as 14% among urban adolescent or rural populations, to 4-7% among college students (Baba et al., 2013; Goel & Chakrabarti, 2010; Gupta, Sarpal, Kumar, Kaur, & Arora, 2013; Ningombam, Hutin, & Murhekar, 2011).

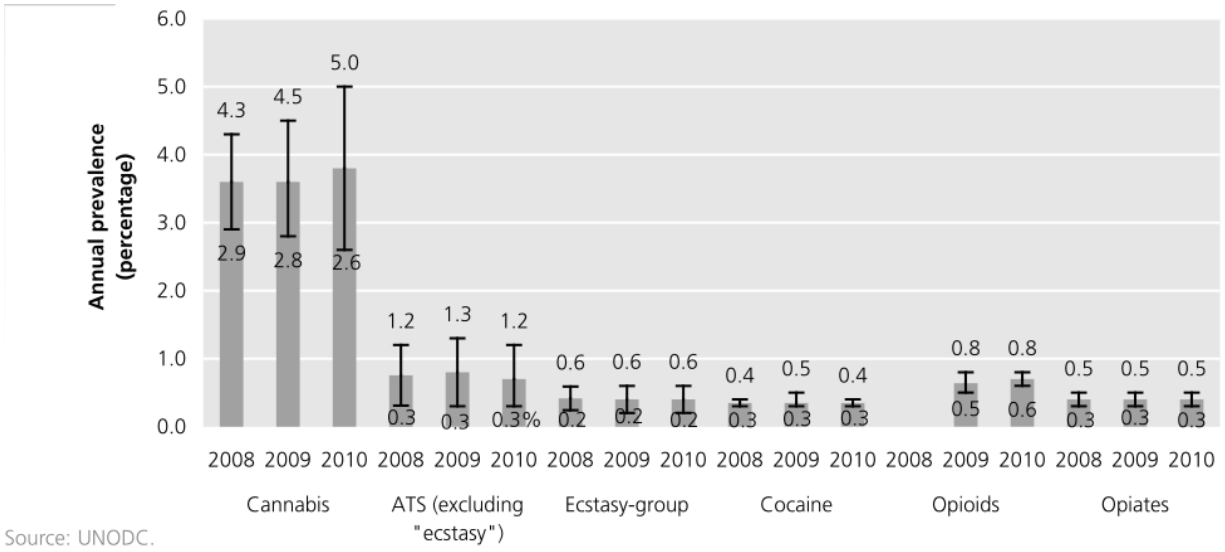



**Figure 2.5.1.** Annual prevalence of drug use among the population 15-64, 2008-2010. Source: United Nations Office on Drug and Crime (UNODC), World Drug Report, 2012. Key: Amphetamine-type stimulants (ATS).


**Figure 2.5.2.** Prevalence of cannabis use in 2010 (or latest year available). Source: United Nations Office on Drug and Crime (UNODC), World Drug Report, 2012. Estimates based on annual report questionnaire data and other official sources.

There is a relatively high rate of cannabis consumption in the U.S., and therefore its NIH finances much of the research on cannabis epidemiology. There are approximately 18.9 million current cannabis users (i.e., used cannabis within the past month), representing about 7.3% of the population (U.S. Department of Health and Humans Services, 2013). Peak cannabis incidence occurred around the mid-1970s, and afterwards there was a sharp decline until a resurgence during the 1990s (Figure 2.5.3). Since 2002, the prevalence of current cannabis use has been relatively stable (6.2% to 7.3%), although in recent years there has been a slight statistically significant increase (Figure 2.5.4). By comparison, the prevalence of other IRDs has been either flat or slightly declining. Adolescence and young adulthood are peak periods of risk for initiating

cannabis smoking (17-18 years), and males are more likely to use than females (Gfroerer, Wu, & Penne, 2002; Wagner & Anthony, 2002a). With respect to racial or ethnic background, White youths are more likely to have used cannabis in the past year (15%), than Hispanics (13%), African-Americans (9%), or Asians (6%) (United States of America, Substance Abuse and Mental Health Services Administration, & Office of Applied Studies, 2002a). Cannabis smokers are also more likely to be found among those with lower academic achievement, the unemployed, and in disadvantaged neighborhoods (United States of America et al., 2002a; United States of America, Substance Abuse and Mental Health Services Administration, & Office of Applied Studies, 2002b, 2004).

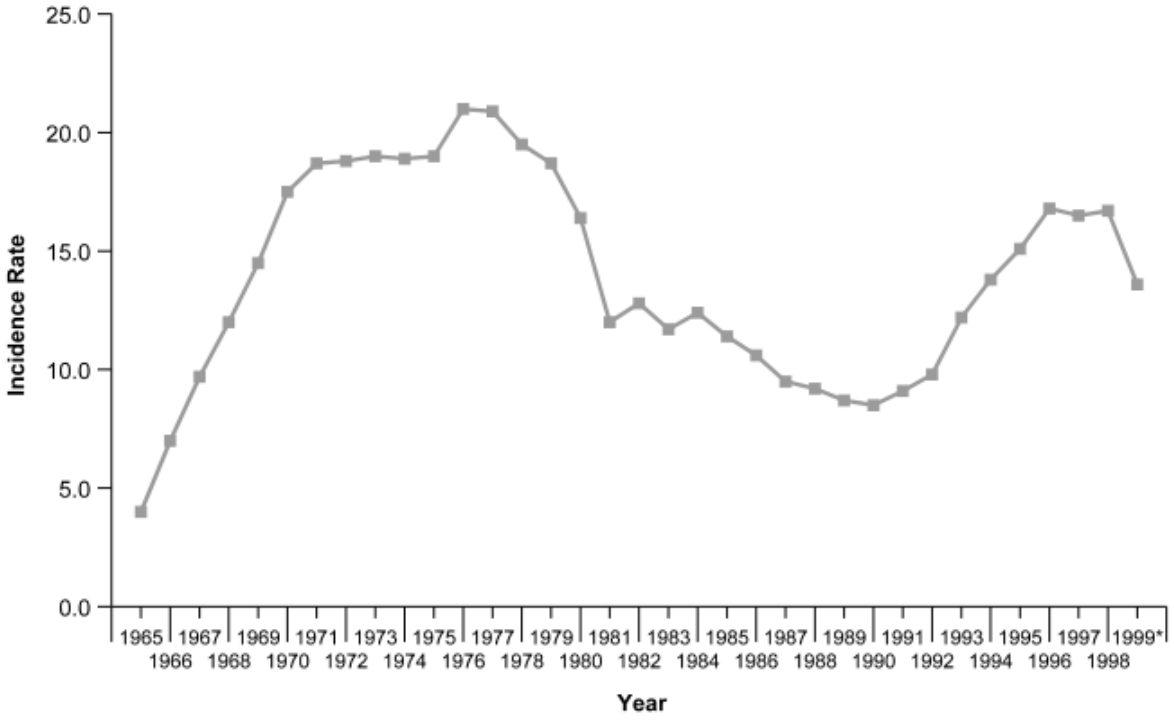
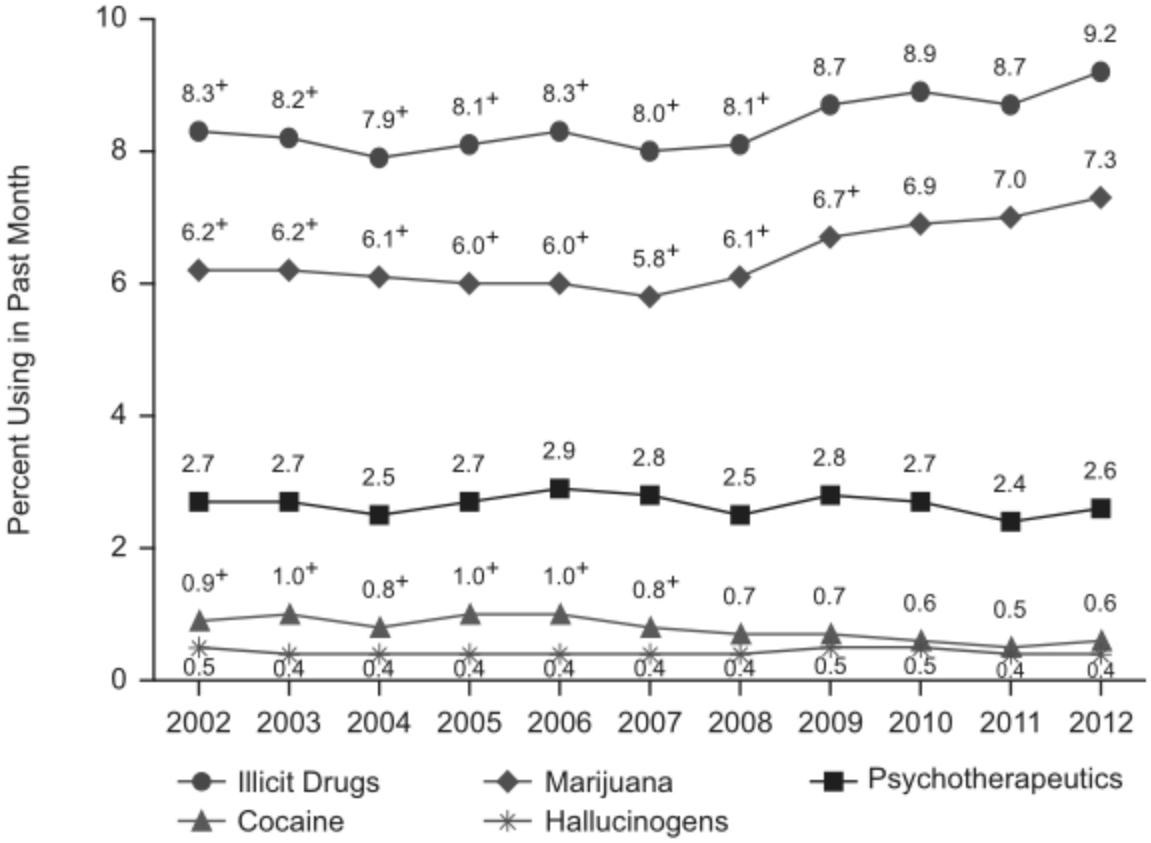



**Figure 2.5.3.** Cannabis incidence rates by year. Source: Gfroerer et al., 2002. Note: The numerator of each rate is the number of persons who first used cannabis in the year, while the denominator is the person-time exposure measured in thousands of years for persons aged 12 or older. *Estimated using 2000 data only.




+ Difference between this estimate and the 2012 estimate is statistically significant at the .05 level.

**Figure 2.5.4.** Past month use of selected internationally regulated drugs (IRDs) among persons aged 12 years or older, 2002-2012. Source: U.S. National Survey on Drug Use and Health, National Findings, 2012.

The epidemiology of cannabis use disorders (CUD) has been less studied than use, thus much of the information comes from studies done in the U.S. and Australia. Based on estimates from the 2012 U.S. National Survey on Drug Use and Health (NSDUH), there were about 4.3 million persons with CUD in the past year (1.7%), which is a trend that has changed little since 2002 (U.S. Department of Health and Humans Services, 2013). Other large epidemiologic surveys in the U.S. and Australia report similar findings (Grant & Pickering, 1998; Hall, Teesson, Lynskey, & Degenhardt, 1999; Kessler et al., 1994; Robins & Regier, 1991; Stinson, Ruan, Pickering, & Grant, 2006). An estimated 8% of cannabis users experience cannabis

dependent within the first ten years, and males are more likely than females to make this transition (Wagner & Anthony, 2002a, 2007; Wittchen et al., 2008). Peak ages for the first CUD occur around the same age as starting to use cannabis, which may indicate a relatively short transition time from first use to disordered use (Stinson et al., 2006; Wagner & Anthony, 2002a).

### 2.5.2. Causes

Suspected causes and underlying theories on why some people use cannabis and then continue to a point when use becomes problematic or pathological can be organized into three broad categories: biological, psychological, and sociological. Most theories of drug use focus on suspected causes that can be generalized to all psychoactive drugs, rather than cannabis-specific. Drug epidemiology studies causes at multiple levels of scale. Biological causes and theories focus mainly on micro-level causes that occur within the individual. Psychological causes and theories can involve both individual-level causes and interactions with group-level cause. Sociological causes and theories deal mainly with group-level or macro-level causes. This does not to say that theories or models exclude aspects of one another. In fact, some integrated theories of drug use overlap, although emphasis or importance might be placed on a specific category. The sheer number of different theories on drug use is too numerous to provide a comprehensive review. However, in this dissertation, I shall attempt to cover a few of the main relevant theories and evidence in each of the three categories. A more comprehensive review of theories on drug use are covered elsewhere (Lettieri, Sayers, & Pearson, 1980; Petraitis, Flay, & Miller, 1995; West, 2001).

*2.5.2.1. Biological Causes and Theories*

Biological theories of drug use tend to focus on physical mechanisms, primarily those involving genes and drug receptors, as an explanation for why some people initiate cannabis and exhibit problematic cannabis use phenotypes (W. Martin, 1980; Schuckit, 1980). These mechanisms have been investigated using experimental studies on animal models, human studies using twin samples, gene linkage analyses, genome-wide association studies (GWAS), and non-invasive imaging techniques.

Suspected genetic determinants of drug use would be carried from conception, and may influence the formation of susceptible drug use phenotypes, with possible contributions of environmental factors. For example, clinical studies of female and male monozygotic twin pairs estimate that around 40 to 48% of the respective total variation in cannabis initiation can be explained by shared genetics, and 59 to 51% for cannabis problems (Kendler, Karkowski, Neale, & Prescott, 2000; Kendler & Prescott, 1998; Rhee et al., 2003; Tsuang et al., 1998; Verweij et al., 2010). This variation between initiation and disordered use may be due to common genetic liabilities contributing more to drug initiation in general, and substance-specific genetic factors possibly playing a larger role in problematic use (Kendler, Jacobson, Prescott, & Neale, 2003; Xian et al., 2008). Genetic linkage analysis studies, which try to narrow the search for drug use-relevant genes to specific chromosomal locations, have found loci for both biologically relevant and potentially novel genes to cannabis dependence, dependence symptoms, and other use pattern phenotypes (e.g., initiation, early use, and frequency of use) (Agrawal et al., 2008a, 2008b; Ehlers, Gizer, Vieten, & Wilhelmsen, 2010; Hopfer et al., 2007). Only two known genome-wide association studies have been currently done, but neither study reported finding

single nucleotide polymorphisms (SNPs) relevant to cannabis use that reached acceptable standards for statistical significance (Agrawal et al., 2011; Verweij et al., 2013).

In addition to genetics, exposure to cannabis can induce pharmacological changes in receptors, neurological pathways, and gene expressions that may influence the development of dysfunctional cannabis use patterns. Prolonged exposure to THC produces sex-dependent downregulation of CB1 brain receptors in both animals and humans, which provides evidence for both the development of tolerance and sources variation by sex. However, this effect appears reversible in humans after several weeks of cessation, and may not complete the whole picture (Hirvonen et al., 2012; B. R. Martin, Sim-Selley, & Selley, 2004). Pre-clinical studies have further found evidence of common and specific pathways related to THC withdrawal via changes in gene expression (Le Merrer et al., 2012). Although much more work is needed to better understand the biological mechanisms underlying cannabis initiation and problematic use, even proponents of biological theories recognize they explain only part of the observed variation, and that environmental events contribute to the overall picture (Schuckit, 1980).

*2.5.2.2. Psychological Causes and Theories*

Psychological causes and theories of drug use emphasize the role of positive and negative reinforcement or individual personality characteristics in the initiation and continuation of drug use (Goode, 1989; Jessor & Jessor, 1980; Lindesmith, 1968; McAuliffe & Gordon, 1980). Drug use behaviors are positively reinforced, and thus repeated, to the extent the experience is pleasurable, while behaviors are negatively reinforced when they relieve or avoid pain, such as to alleviate withdrawal symptoms. Pre-clinical work finds THC activates the same mesolimbic dopamine system hypothesized responsible for the rewarding and reinforcing effects of multiple

drug classes (Gardner & Vorel, 1998; Tanda & Goldberg, 2003). In humans, cannabis users under both naturalistic and laboratory environments commonly report experiencing more positive feelings, such as euphoria, relaxation, happiness, sociability, creativity, and sexual pleasure/arousal, than negative feelings of paranoia, anxiety, depressed mood, or irritability (B. Green, Kavanagh, & Young, 2003). Volunteers under controlled laboratory conditions report experiencing positive reinforcing properties of both smoked cannabis and oral-THC (Chait & Zacny, 1992; Mendelson & Mello, 1984). In another study of primarily opioids users, cannabis was reported as positively reinforcing after the very first use, in contrast to subjectively described effects of nicotine (Haertzen, Kocher, & Miyasato, 1983).

The degree to which cannabis is reinforcing might manifest as shorter lag times from first use of the drug to the second use, third, fourth, and so on, prior to other processes (e.g., withdrawal) exerting an influence on the process that drives frequency of drug use. This topic has been informed by early work by Becker (1953) on the experiences of first-time or novice cannabis users, and most recently by Agrawal and colleagues on the initial reactions towards cannabis (Agrawal, Madden, Bucholz, Heath, & Lynskey, 2014; Agrawal, Madden, Martin, & Lynskey, 2013). Notwithstanding this research, time from first cannabis use to more frequent use (e.g., monthly use) has served as a proxy measure of this process. For example, Crowley and colleagues (1998) found patients in treatment programs for delinquent or substance use problems transitioned from first use of tobacco or cannabis to regular (monthly use) within about a year, while the same transition for alcohol took slightly longer (mean = 2 years). Other studies have reported either shorter or comparable transition times from first to regular cannabis use as compared to alcohol, tobacco, and other "illicit" drugs (Ridenour, Lanza, Donny, & Clark, 2006; Wittchen et al., 2008). Negative reinforcement is commonly associated with the presence of a

withdrawal syndrome. While cannabis withdrawal was previously considered to be of little clinical significance, the current consensus is otherwise (Budney et al., 2004).

Theories emphasizing the role of personality characteristics as determinants of starting to use drugs have focused on traits of deviance, impulsivity, and risk taking. Here, by 'deviant' the meaning is not pejorative, but refers to behaviors that are outside the norms of the majority. Jessor and Jessor (1980) hypothesized a social-psychological structure called 'problem behavior proneness', whereby drugs users would be more likely to have "a concern with personal autonomy, a lack of interest in the goals of conventional institutions like church and school, a jaundiced view of the larger society, and a more tolerant view of transgression" (Jessor & Jessor, 1980, p. 109). These personality traits shape and are shaped by the perceived social environment where the compatibility and support of peers and parents exert the most influence. Problem behavior proneness has some direct empirical support for cannabis use (Jessor, Chase, & Donovan, 1980; Jessor, Jessor, & Finney, 1973). However, much of the current literature has focused specifically on conduct problems and other externalizing behaviors as predictors of drug use (Fergusson, Boden, & Horwood, 2008; Krueger et al., 2002; Miles, van den Bree, & Pickens, 2002; Schubiner et al., 2000).

Impulse control problems may also underlie such deviant behaviors, in which such individuals are more likely to take risks, and choose more immediate gratification over long-term negative consequences. Both experimental and observational evidence support findings that individuals with higher impulsivity or adolescents with attention deficit hyperactivity disorder (ADHD) are more likely to use cannabis and become cannabis dependent (Day, Metrik, Spillane, & Kahler, 2013; Kong et al., 2013; C. A. Martin et al., 2002; McDonald, Schleifer, Richards, &

de Wit, 2003; Miles et al., 2001; Murphy, Barkley, & Bush, 2002; Rios-Bedoya, Wilcox, Piazza, & Anthony, 2008).

*2.5.2.3. Sociological Causes and Theories*

While biological and psychological causes and theories focus on individual-level differences of scale, sociological causes and theories attempt to explain drug use in terms of structural factors in society and social relations (Goode, 1989). For example, adolescents who associate with more deviant and/or drug-using peers are at a greater risk for later cannabis involvement (Dishion & Loeber, 1985; Fergusson, Horwood, & Swain-Campbell, 2002; Hofler et al., 1999; Lynskey, Fergusson, & Horwood, 1998; von Sydow, Lieb, Pfister, Hofler, & Wittchen, 2002). Theories that emphasize peer influence explain drug use as a learned behavior, where youths may seek out deviant groups that share underlying values, but are also themselves socialized into the drug subculture that has its own conduct norms (B. D. Johnson, 1980; Kandel, 1980; Oetting & Beauvais, 1987; Oetting & Donnermeyer, 1998; Sutherland, 1939). Aside from peers, parents are another source of influence on drug use that has been studied. Higher levels of parental monitoring and poorer parenting practices may increase the chance of trying cannabis and initiation (Bohnert, Anthony, & Breslau, 2012; J. S. Brook et al., 1998; C. Y. Chen, Storr, & Anthony, 2005; Chilcoat & Anthony, 1996; Hansen et al., 1987). Self-control theory attributes inadequate parental socialization and monitoring as leading to children having low self-control (i.e., more impulsivity), and thus greater likelihood of using drugs (Gottfredson & Hirschi, 1990). In addition to parental influences, cannabis and drug users are less likely to go to church and be involved in school (J. S. Brook, Adams, Balka, & Johnson, 2002; C. Y. Chen, Dormitzer, Bejarano, & Anthony, 2004; Cochran, Wood, & Arneklev, 1994; Dornbusch, Erickson, Laird, &

Wong, 2001). This has led some sociologists to theorize that drug use may be due to inadequate social control or weak attachments to parental, religious, and school institutions (Elliott, Huizinga, & Ageton, 1985; Elliott, Huizinga, & Menard, 1989; Goode, 1989; Hirschi, 1969). This lack of social control can occur on the neighborhood level, and is referred to as a social disorganization model, where deviant behaviors like drug use flourish because members of the neighborhood are unwilling or unable to place controls on such behaviors (Goode, 1989; Petraitis et al., 1995). Cannabis users are found to cluster within certain neighborhoods, and living in more disordered or disadvantaged neighborhoods are found to increase the risk of being offered cannabis and using (Bobashev & Anthony, 1998, 2000; Crum, Lillie-Blanton, & Anthony, 1996; Wells, Degenhardt, Bohnert, Anthony, & Scott, 2009; Wilson, Syme, Boyce, Battistich, & Selvin, 2005).

### 2.5.3. Mechanisms

The mechanisms of cannabis smoking describe the inter-related processes that link the initial cannabis use experience to repetition of the cannabis use behavior until the development of a pathological compulsion to use cannabis that may not be entirely volitional in the sense that there is an attenuation or 'loss of control' over use. This general model of the natural history of drug use grew from work by Robins (1980), who investigated the predictors of different drug-stage transitions among heroin-using Vietnam Veterans (Helzer, Robins, & Davis, 1976). More recently, Anthony (2010) commented upon this model, where the first step in the process of becoming a drug user is having an opportunity to use the drug. After the onset of drug use there is an accumulation of drug use experiences manifested in the frequency of occasions. At some later point, there begins the first signs or symptoms of a drug problem (e.g., experiences of

tolerance or craving), which occur prior to the full expression of a drug use disorder. These drug problems then can influence or feedback into the process of repetitious drug use, which may further drive the dependence process. However, transition along this continuum is not certain for all drug users, and many may stop spontaneously or due to an intervention, while still others may continue to use drugs without experiencing dysfunction. Nonetheless, heavy or chronic cannabis smoking (with or without dependence) might lead to adverse health consequences and/or social disadvantage.

*2.5.3.1. Opportunity to Try Cannabis*

The earliest stage of cannabis use is marked by the initial opportunity to use cannabis. In the U.S., as many as half of the population report at least one opportunity, which typically occurs around age 16 (Van Etten et al., 1997). Among those with an opportunity to try cannabis, around one-third do so within the first year (Van Etten & Anthony, 1999; Van Etten et al., 1997). Other investigations, conducted mostly in the U.S. and Latin America, have tried to identify sources of variation in who does and does not have a chance to use cannabis (C. Y. Chen, Dormitzer, Gutierrez, et al., 2004; Delva et al., 1999; Neumark, Lopez-Quintero, & Bobashev, 2012; Rosenberg & Anthony, 2001a; Stenbacka, Allebeck, & Romelsjö, 1993; Storr, Chen, & Anthony, 2004; Storr, Wagner, Chen, & Anthony, 2011; Wagner & Anthony, 2002b). Males, those who are less religious or engaged in school, those who are more aggressive or misbehave, and prior use of tobacco and alcohol are all associated with either being offered cannabis or have an opportunity at an earlier age (Van Etten, Neumark, & Anthony, 1999; Wells et al., 2011). Social environment may also play a factor. Youths living in disadvantaged neighborhoods, have parents who use drugs or are less engaged, and who have cannabis-using friends are more likely

to have opportunities (Benjet et al., 2007; Crum et al., 1996; Pinchevsky et al., 2012; Storr, Chen, et al., 2004). Given a chance to try cannabis, a relatively high proportion end up using (65%), which is greater than for cocaine or heroin, but similar to hallucinogen use (Van Etten & Anthony, 1999).

*2.5.3.2. Cannabis Use and Escalation to Frequent and Problematic Use*

The natural course of cannabis use begins during the period of adolescence, where the risk of using cannabis starts to increase at 12-13 years, reaches a peak by ages 17-18, and then has few onsets after 21-22 years (Tucker, Ellickson, Orlando, Martino, & Klein, 2005; von Sydow et al., 2002; Wagner & Anthony, 2002a; Wittchen et al., 2008). Researchers using longitudinal growth modeling have tried to identify trajectory patterns of cannabis use from those who start in adolescence though young adulthood. For example, Schulenberg and colleagues (2005) identified five main groups: 1) a rare group that had some use, but never frequent, 2) a fling group characterized by a brief period of frequent use, followed by little or no later use; 3) increasers, whose frequency of cannabis use escalated over time; 4) decreasers, who frequently used in the beginning, but then ceased or decreased use over time, and 5) chronic users who became frequent users and continued to be so throughout follow-up. Other studies have identified similar groupings characterized by low-level, occasional users, those who escalate over time, those whose use declines as they get older, and chronic users whose level of use remain high (J. S. Brook, Lee, Brown, Finch, & Brook, 2011; Caldeira, O'Grady, Vincent, & Arria, 2012; Tucker et al., 2005; Windle & Wiesner, 2004).

The developmental periods of a cannabis use disorder are also around the same period of adolescence and young adulthood (15-20 years), with an expected, slightly higher average peak

of onset risk around 17-19 years (Stinson et al., 2006; Wagner & Anthony, 2002a; Wittchen et al., 2008). When a cannabis use disorder does develop, it usually does so within the first few years after onset, and it much less likely to develop after age 25 (C. Y. Chen, O'Brien, & Anthony, 2005; Wagner & Anthony, 2002a). Which features of problematic cannabis use emerge first has been previously studied by Rosenberg and Anthony (2001b), comparing non-dependent and dependent cannabis users. They found cannabis users experienced subjective loss of control over use was one of the earliest and most frequent features, and experiences of hazardous use followed fairly quickly after onset (within the first year). Tolerance emerged relatively later than previously expected, and withdrawal was one of the least and later features experienced. Among cases of cannabis dependence, using larger amounts than intended and hazardous use emerged early in the process, suggesting a heterogeneous course of problematic use.

*2.5.3.3. Secondary Consequences of Cannabis Smoking*

Part of the natural course of cannabis smoking may include secondary outcomes leading to increased morbidity or mortality. There have been no known reported cases of fatal cannabis overdose, and there is some evidence that cannabis users are *less likely* to die from a drug-related event (Nyhlén, Fridell, Bäckström, Hesse, & Krantz, 2011). However, similar to persistent tobacco smoking, the risk of early mortality may accumulate over time due to other causes.

Only a few studies have looked at all-cause mortality and cannabis use. Neumark, Van Etten, and Anthony (2000) observed that those with a drug dependence diagnosis were 2-3 times as likely than those without such a diagnosis to die prematurely (average of 22 years), adjusted for age, race, smoking status, and an alcohol use disorder. Although cannabis dependence was grouped together with dependence on other drugs, those who only had cannabis dependence

made up 65% of all drug dependence cases, and 45% of deceased cases. Three other studies have examined cannabis all-cause mortality specifically. In a Swedish study of a treatment population, patients with a primary cannabis use disorder had a standardize mortality ratio (SMR) of 5.3 (Arendt, Munk-Jørgensen, Sher, & Jensen, 2011). This was much lower than for heroin (SMR=16.9), and cocaine (SMR=7.0), but similar to amphetamines (SMR=5.4). Another study of Danish males followed over 35-years found cannabis was associated with an elevated mortality hazard (hazard ratio, HR=4.3) that was similar for stimulants (HR=4.4), but less than for opioids (HR=2.8) (Davstad, Allebeck, Leifman, Stenbacka, & Romelsjö, 2011). The authors attributed the lower mortality risk of opioids to the prominence of stimulant use in Denmark. Finally, a U.S. based study of patients in a large health service organization reported a higher mortality risk for males of weekly and daily cannabis smokers (relative risk, RR=1.5 and 1.4, respectively), but not for females (Sidney, Beck, Tekawa, Quesenberry, & Friedman, 1997).

Cannabis may contribute to increased morbidity and mortality through physiological disease and accidental injury. Acute effects of cannabis smoking may include triggering of strokes and myocardial infarction episodes, especially in susceptible individuals (Desbois & Cacoub, 2013; Mittleman, Lewis, Maclure, Sherwood, & Muller, 2001). Intoxication can also impair reaction times and impair driving, leading to an increased risk of automobile crashes (Bedard, Dubois, & Weaver, 2007; Blows et al., 2005; Callaghan, Gatley, et al., 2013; Drummer et al., 2003; Fergusson, Horwood, & Boden, 2008). Long-term effects of cannabis smoking on the risk of lung or other cancers has been less convincing based on epidemiologic studies (Hashibe et al., 2005; Mehra, Moore, Crothers, Tetrault, & Fiellin, 2006). This may be due in part to difficulties measuring lifetime cumulative exposure and sorting out the influence of tobacco smoking, Two recent case-control studies reported increased cannabis joint-years was

associated with a higher odds of lung cancer, even after controlling for tobacco pack-years (Aldington et al., 2008; Berthiller et al., 2008). These findings were supported by a prospective study that found "heavy" cannabis smoking (defined as 50 or more uses) was associated with a two-fold excess risk of lung cancer in a sample followed for 40-years (Callaghan, Allebeck, & Sidorchuk, 2013). Only one study has purported cannabis use *decreases* the risk for lung and other cancers (A. Chen et al., 2008).

Much of the literature on long-term effects of cannabis on mental health has focused on cognitive deficits and psychosis, with a lesser extent mood disorders and suicide risk. Heavy cannabis users exhibit cognitive deficits and impaired memory as compared to controls, but it is unclear whether these effects are long-lasting or continue after cannabis use is discontinued (Jager, Block, Luijten, & Ramsey, 2010; Pope, Gruber, Hudson, Huestis, & Yurgelun-Todd, 2001; Pope & YurgelunTodd, 1996; Solowij et al., 2002). Among psychiatric disorders, cannabis use appears to increase the risk of psychosis, but there has been less consistent evidence for mood disorders (Arseneault, Cannon, Witton, & Murray, 2004; Degenhardt, Hall, & Lynskey, 2003; T. H. M. Moore et al., 2007). Suicide risk is elevated among cannabis users, but it is still unclear whether if it is caused by cannabis, a consequence, or confounded by other factors (Beautrais, Joyce, & Mulder, 1999; Lynskey et al., 2004; T. H. M. Moore et al., 2007; Pedersen, 2008; Rasic, Weerasinghe, Asbridge, & Langille, 2012; Wilcox & Anthony, 2004).

### 2.5.4. Prevention and Control

There is a societal need for prevention and treatment of cannabis problems. In the U.S., an estimated 957,000 people received treatment for cannabis use in 2012, more than for cocaine and heroin (650,000 and 450,000, respectively), but slightly behind treatment for pain reliever

use (973,000), and much lower than for alcohol (2.4 million) (U.S. Department of Health and Humans Services, 2013). Survey samples of U.S. high-school seniors from 1977 to 2005 indicate that among past-year cannabis users, at least half felt they either should stop or reduce their use (Terry-McElrath, O'Malley, & Johnston, 2008). Control efforts are directed to developing interventions and treatments to treat CUDs and reduce their incidence. Cannabis is criminalized in most countries, and therefore those presenting for treatment may be there due to a court order. The ethics of legally-coerced cannabis treatment has been debated, yet some evidence points to better outcomes as compared to non-coerced persons (Caplan, 2006; Copeland & Maxwell, 2007; Miller & Flaherty, 2000).

Primary prevention programs seek to reduce the incidence of CUDs by preventing the onset of cannabis smoking. Two systematic reviews of school-based interventions tried to identify characteristics of cannabis prevention programs that were the most effective (Lemstra et al., 2010; Porath-Waller, Beasley, & Beirness, 2010; Tobler, Lessard, Marshall, Ochshorn, & Roona, 1999). Increased effectiveness was seen in programs that administered to larger samples, used multiple prevention models, were longer in duration, used facilitators other than teachers, targeted high-school students, and stressed interactive social competency development rather than lecture-based knowledge improvement. However, different conclusions were drawn when both school-based and non-school based primary prevention programs were studied (Norberg, Kezelman, & Lim-Howe, 2013). Programs that targeted all-drugs, younger adolescents (10-13 years), multiple modalities (i.e., school, family, and peer-based), and were shorter in duration with multiple booster sessions had greater effect sizes. These effect sizes ranged from trivial to large, with most studies reporting trivial to small effects.

A few of the more studied treatment programs for CUDs and their conceptual framework are covered here. Cognitive behavioral treatment (CBT) is based on social learning theory and is designed to improve the coping skills, and may be appropriate to those already seeking to change (Stephens, Roffman, Copeland, & Swift, 2006). CBT can be paired with motivational enhancement treatment (MET), which was designed to reduce ambivalence and increase motivation to change for those cannabis dependent users who may be uncertain change is needed. While treatment-outcome studies support CBT/MET over delayed treatment controls (DTCs), these studies have yet to show CBT/MET to be superior over other treatments (Budney, Higgins, Radonovich, & Novy, 2000; Copeland, Swift, Roffman, & Stephens, 2001; Dennis et al., 2004; Stephens, Roffman, & Curtin, 2000; Stephens, Roffman, & Simpson, 1994). For example, in the Cannabis Youth Treatment (CYT) Study, Dennis and colleagues (2004) conducted a randomized trial comparing CBT/MET to four alternative treatments on outcomes of days abstinent and percent in recovery in a sample of adolescents with cannabis related disorders. While all treatments produced similar results in outcomes, they found CBT/MET was most cost-effective after controlling for level of severity. An alternative approach frequently studied is contingency management (CM) interventions, which rely on positive/negative reinforcement/punishment strategies to induce change. For example, subjects might receive a voucher of monetary value for clear urine samples, or have the value of the voucher reduced if incurring relapse. Contingency management, especially voucher-based studies, show a positive effect on abstinence and may improve effectiveness when combined with CBT and MET strategies (Budney et al., 2000; Budney, Moore, Rocha, & Higgins, 2006; Carroll et al., 2006; Kadden, Litt, Kabela-Cormier, & Petry, 2007).

## 2.6. Cannabis Smoking, Depression, and Functional Impairment

### 2.6.1. The Burden and Epidemiology of Depression

Before discussing the literature on the relationship between cannabis smoking and depression, some background on the diagnosis, epidemiology, and public health burden of depression will be helpful. Major depression is characterized by a sustained period of low mood or markedly diminished interest or pleasure in most activities (i.e., anhedonia), and can be accompanied by difficulties with sleep, weight or appetite, concentration, energy, or recurrent thoughts of suicide (see Table 2.5.1 for DSM-IV diagnostic criteria; American Psychiatric Association, 1994). The World Health Organization World Mental Health Surveys (WHO-WMHS) projected as many as one in three people by the age of 75 will experience a mood disorder in their lifetime, with a greater prevalence among high income countries like the U.S., France, the Netherlands, and New Zealand (Kessler et al., 2007). Mood disorders tend to have onsets in late 20s to early 40s, and there may be evidence of an increased prevalence among younger cohorts compared to older cohorts (Fombonne, 1994; Kessler et al., 2003, 2007; Klerman & Weissman, 1989; Weissman et al., 1996). Females are more likely than males to be depressed (Hankin et al., 1998; Kessler, McGonagle, Swartz, Blazer, & Nelson, 1993; Lewinsohn, Hops, Roberts, Seeley, & Andrews, 1993; Piccinelli & Wilkinson, 2000). Other characteristics, such as lower income, lower educational attainment, unemployment, divorced or separation, other psychiatric disorders, and drug use are associated with depression (Anthony & Petronis, 1991; Blazer, Kessler, McGonagle, & Swartz, 1994; Hasin, Goodwin, Stinson, & Grant, 2005; Kessler et al., 2011; Weissman et al., 1996). The public health burden is considerable. Depression is the leading cause of disability adjusted life years (DALYs) among mental health disorders, and it is projected to be the second largest overall cause of DALYs by

2020 (Lopez, Mathers, Ezzati, Jamison, & Murray, 2006; Murray & Lopez, 1997). Major depression accounted for 8% of global years lived with disability in 2010, and was the leading contributor to the burden of suicide and ischemic heart disease (Ferrari et al., 2013). The economic toll, in terms of treatment costs and lost productivity, exceed well over $80 billion dollars annually in the United States (Greenberg et al., 2003).

**Table 2.6.1.** Major Depressive Episode Diagnostic Criteria Based on the *Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition* (DSM-IV)

| |
|---|
| **A.** Five (or more) of the following symptoms have been present during the same two-week period and represent a change from previous functioning. At least one of the symptoms is (1) depressed mood or (2) loss of interest or pleasure.<br>1) Depressed mood most of the day, nearly every day, as indicated by either subjective report or observation made by other.<br>2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day.<br>3) Significant weight loss when not dieting or significant gain, or decreased or increased appetite nearly every day.<br>4) Insomnia or hypersomnia nearly every day.<br>5) Psychomotor agitation or retardation nearly every day.<br>6) Fatigue or loss of energy nearly every day.<br>7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).<br>8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).<br>9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide. |
| **B.** The symptoms do not meet the criteria for a mixed episode. |
| **C.** The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. |
| **D.** The symptoms are not due to the direct physiological effects of a substance (for example, a drug of abuse, a medication), or a general medical condition. |
| **E.** The symptoms are not better accounted for by bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicide ideation, psychotic symptoms or psychomotor retardation. |

### 2.6.2. Suspected Mechanisms Linking Cannabis Smoking and Depression

In clinical and representative household samples, depression and cannabis smoking tend to co-occur more often than one would expect by chance alone (Alpert, Maddocks, Rosenbaum, & Fava, 1994; C. Y. Chen et al., 2002; Degenhardt, Hall, & Lynskey, 2001; Grant, 1995; Rey, Sawyer, Raphael, Patton, & Lynskey, 2002; Rowe, Fleming, Barry, Manwell, & Kropp, 1995). For example, in the nationally representative U.S. National Longitudinal Alcohol Epidemiologic Survey (NLAES), major depression was associated with a six-fold higher odds of a cannabis use disorder (Grant, 1995). More modest or null associations have been reported when differentiating between dependent and non-dependent cannabis use, and after controlling for sex, other background factors, tobacco, and alcohol use (C. Y. Chen et al., 2002; Degenhardt et al., 2001).

Findings of co-morbidity from cross-sectional studies are suggestive of a causal relationship, but additional evidence is needed to assure the suspected exposure preceded the outcome in time. In addition, other considerations aid in making causal inferences, such as the nine described by Sir Bradford Hill (1965): 1) strength of the association; 2) consistency of the evidence; 3) specificity of exposure to the disease; 4) temporality; 5) presence of biological (dose-response) gradient; 6) plausibility with respect to biological mechanisms; 7) coherence with what is already known; 8) experiment evidence; 9) analogy from similar evidence. In light of these considerations, experimental and epidemiologic research designs have attempted to answer two questions, while trying to rule out a third: 1) Does cannabis smoking cause depression? 2) Does depression cause cannabis smoking? 3) Can the link between cannabis smoking and depression be explained by some third factor or process? Two main avenues of research have been applied to these questions. One avenue looks at biological mechanisms linking the neurological underpinnings of mood dysregulation and the endocannabinoid system.

The other proposes indirect psychological or social factors connect cannabis smoking to depressed mood, or that cannabis is used to alleviate negative affect.

### 2.6.3. Biological Mechanisms

Pre-clinical studies, mostly using rodent models, have tried to understand the relationship between cannabinoids, their receptors, and mechanisms involved with mood regulation. Cannabinoid receptors (CB1) are expressed on neurons throughout the central nervous system, including the mesolimbic areas of the brain, thought to be involved in stress-response and emotional regulation through the hypothalamic-pituitary-adrenocortical (HPA) system (Herkenham et al., 1991; Holsboer, 2000; Weidenfeld, Feldman, & Mechoulam, 1994). Direct stimulation of CB1 receptors or indirect stimulation by inhibiting the metabolism of endocannabinoids produces antidepressive-like effects, possibly through stimulation of neurons that increase transmission of noradrenaline (NA) and serotonin (5HT) (Gobbi et al., 2005; M. N. Hill & Gorzalka, 2005; Matthew N Hill & Gorzalka, 2005). Inhibiting reuptake of these neurotransmitters is the basis of many current anti-depressant drugs (Gobbi et al., 2005; Schildkraut, 1965). Mice lacking CB1 receptors generally exhibit more depressive-like and anxiety-like behaviors, but results can vary under different environment conditions, especially when stress is induced (M. Martin, Ledent, Parmentier, Maldonado, & Valverde, 2002; Zanettini et al., 2011). The biological evidence would appear to support an anti-depression role for cannabinoid action and receptors.

The role of the endocannabinoid system in the regulation of emotion and mood is complex and not fully understood. Low doses of cannabinoid agonists can induce anxiolytic-like responses in mice, but larger doses can produce anxiogenic effects (Kathuria et al., 2003; Patel &

Hillard, 2006; Rubino, Realini, et al., 2008). Further, cannabinoid *antagonists* also have been shown to produce anxiolytic and antidepressive-like effects (Navarro et al., 1997; Shearman et al., 2003; Tzavara et al., 2003). Human clinical trials of a CB1 antagonist called rimonabant were ceased after subjects experienced elevated anxiety and depression (Scheen, Finer, Hollander, Jensen, & Van Goal, 2006; Van Gaal, Rissanen, Scheen, Ziegler, & Rossner, 2005).

There may also be important and overlooked sex-dependent and maturation-dependent variation in effects of cannabinoids on mood. During adolescence, the human brain continues to develop and may be vulnerable to changes induced by exogenous agents like cannabis (Rice & Barone, 2000; Schneider & Koch, 2003; Schneider, 2008). Following along this line, Rubino and colleagues (2008) found that administration of THC in adolescent rats and then left to mature had sex-dependent reduction in CB1 receptor density and G-protein coupling (which is necessary for the CB1 receptor to be "active") in the amygdala, ventral tegmental area, and nucleus accumbens areas of the brain involved in emotional processing and reward. Female rats administered a THC-agonist exhibited no effects on anxiety-like responses, but they did display more "behavioral despair" and anhedonia, while males only showed anhedonia. Bambico and others (2010) similarly found that administration of a CB1 receptor agonist produced anxiety-like and depressive-like behaviors in adolescent-treated, but not adult-treated rats. Both low and high doses led to rats performing more poorly on the forced swim and sucrose preference tests used as models for behavioral despair and anhedonia, respectively. Anxiety-like differential responses were produce for high doses only.

### 2.6.4. Psychosocial Mechanisms

An alternative mechanism of cannabis toxicity might involve psychosocial factors, whereby cannabis involvement initiates or exacerbates a chain of adverse life outcomes, which in turn increase the risk of depression (Degenhardt et al., 2003). Lower educational attainment, unemployment, greater financial strain, difficulties maintaining and establishing close relationships, legal problems, illegal drug involvement, stressful life events, and other difficulties assuming adult roles have been observed to be more common among heavy cannabis smokers and predictive of depression (Colman & Ataullahjan, 2010; Fergusson & Boden, 2008; Fergusson & Horwood, 1997; B. E. Green & Ritter, 2000; Kandel, Davies, Karus, & Yamaguchi, 1986; Marmorstein & Iacono, 2011; Weich & Lewis, 1998). Depression can also contribute to lower educational attainment (Fletcher, 2008), unemployment (Luo, Cowell, Musuda, Novak, & Johnson, 2010), and marital disruption (Briscoe & Smith, 1973; Fincham, Beach, Harold, & Osborne, 1997), suggesting potential feedback loops between depression and poor psychosocial outcomes.

Another perspective theorizes that depression might increase the incidence of cannabis smoking via self-medication to alleviate negative affect or disturbances in appetite or sleep that are among depression's clinical features (Khantzian, 1997). This idea would appear plausible considering the above mentioned pre-clinical evidence for cannabinoids producing antidepressive effects, human studies of the positive affective experiences of cannabis intoxication, and self-reported motives of alcohol and drug use initiation among cases of dysphoric mood (Bambico, Duranti, Tontini, Tarzia, & Gobbi, 2009; B. Green et al., 2003; Mueser, Drake, & Wallach, 1998). However, most of the epidemiologic evidence has failed to show that individuals with depression at baseline are more likely to start using cannabis (Arendt

et al., 2007; Bardone et al., 1998; J. S. Brook et al., 1998; Kandel & Chen, 2000; Kandel et al., 1986; Patton et al., 2002).

### 2.6.5. Epidemiologic Evidence for Cannabis as a Possible Cause of Depression

A few selected cross-sectional studies are informative as to whether cannabis smoking predicts later depressed mood. Normally, this is not the case when surveys measure both the suspected exposure and outcome at a single time point, and there is no other information from which to guide what event came first. However, chronological assumptions can be made when participants are asked to self-report the age when specific events occur, such as the onset of drug use and depression. For example, Chen, Wagner, and Anthony (2002) used age of onset information to account for the temporal sequence between major depressive episode (MDE) and cannabis dependence in data from the U.S. National Comorbidity Survey (NCS). They found cannabis smoking males, with or without daily tobacco smoking, had a modest excess risk of MDE. Only daily tobacco smoking, non-dependent cannabis-using females were at an increased risk of MDE over-and-above the excess risk for depression among females.

A similar approach was employed by this dissertation's author in a paper by de Graaf and colleagues (2010) using data from the WHO World Mental Health Surveys (WHO-WMHS). We studied the association between early-onset cannabis use defined any use prior to age 18 years and the first occurrence of a sustained spell of depressed mood in adulthood (18 years or older) among all adults. In our analysis, we excluded those with a depression spell onset prior to adulthood as a violation of the temporal assumptions of the model. A modest association between early-onset cannabis use and depression spells was observed (odds ratio, OR=1.5), adjusting for sex, age, tobacco use, and other mental health problems. After further adjustment for conduct problems, there was no longer a statistically significant effect estimate.

Another study, which held constant shared genetic and environmental factors through a twin study design, found no evidence that early-onset cannabis use predicted major depressive episode (Lynskey et al., 2004). However, they did find that early-onset cannabis use was associated with attempted suicide. While caution is warranted when drawing causal inferences from cross-sectional study designs, these studies do have advantages in that they have no sample attrition, take less time to complete, and can more easily inform across a broader age span than typical longitudinal study designs. Nevertheless, prospective studies are considered superior in terms of making causal inferences with respect to temporally measured exposures and outcomes, and can be better suited to study time-varying covariates when multiple observations are made over time. These studies are reviewed below.

The prospective relationship between adolescent cannabis smoking and the risk of depression in adolescence or young adulthood is unclear. Perhaps the earliest longitudinal study to test this hypothesis was in a representative sample of public high school students in New York State (Paton, Kessler, & Kandel, 1977). Cannabis use did not predict depressed mood one year later, or in a later follow-up at age 24-25 years (Kandel et al., 1986). Past-year cannabis use at age 15 was associated with depression one year later at age 16 in unadjusted models (odds ratio, OR=2.7), but not in adjusted models (OR=1.2) in a New Zealand cohort, the Christchurch Health and Development Study (CHDS;(Fergusson, Lynskey, & Horwood, 1996). Follow-up of this cohort to age 20-21 did reveal higher rates of depression with increasing cannabis involvement (Fergusson et al., 2002). Contrasting this trend, weekly cannabis smoking in females, but not males, was associated with an almost two-fold excess risk of depression (OR=1.9) in an Australian cohort by age 20-21 years, but later follow-up to 24 years showed evidence of no effect of either occasional or weekly cannabis use and depression (Degenhardt et al., 2013;

Patton et al., 2002). However, the Degenhardt et al. study used a different depression measure and did not report separate estimates by sex.

The timing of cannabis onset (early vs. late) may modify the relationship with depression. For instance, cannabis use in childhood (by age 14) and in mid-adolescence (14-16 years) predicted a modest excess risk of a major depressive disorder (MDD) (OR=1.6 and 1.4, respectively) by late 20s, but cannabis use in early 20s did not (J. S. Brook et al., 2002). In another study, both early and late adolescent cannabis onset (before 14 vs. after) was associated with depression and anxiety in young adulthood (21 years) for frequent cannabis users (ORs=2.3 and 3.0), but no association was observed for early or late onset, occasional users (Hayatbakhsh et al., 2007).

Prospective studies of adult samples have likewise been inconsistent. For example, having a cannabis use disorder, but no depression symptoms, at baseline was associated with a four-fold increased risk of experiencing at least one depression symptom after a 14-16 year follow up in adults 18 years or older from the Baltimore Epidemiologic Catchment Area (ECA) Study (Bovasso, 2001). In another study, any cannabis use was associated with major depression in an adult sample from the Netherlands after a three-year follow-up, but differences were not seen when separating cannabis users by frequency levels (van Laar, van Dorsselaer, Monshouwer, & de Graaf, 2007). These positive findings are weighed against others who have found no evidence of an association, or report null results after accounting for confounding factors (Harder, Morral, & Arkes, 2006; Manrique-Garcia, Zammit, Dalman, Hemmingsson, & Allebeck, 2012; Pedersen, 2008).

Variation among prospective studies may be due to a number of factors. Differences in the age range of exposure studied (adolescence vs. adult), cumulative cannabis exposure or

phenotype (any cannabis use, heavy use, dependent use), length and number of follow-up points, measurement of depression (symptom scale vs. clinical diagnosis), and degree of adjustment for potential confounding factors could explain some of the variation in estimates. Nevertheless, a recent meta-analysis of 10 longitudinal studies concluded an overall very modest positive effect of cannabis smoking on depression (OR=1.2), and a slightly larger effect for heavy cannabis use (8 studies; OR=1.6; Lev-Ran et al., 2013).

### 2.6.6. Functional Impairment, Depression, and Cannabis Use

Regardless of the causal relationship between cannabis smoking and depression, it may still be possible that cannabis smoking exacerbates depressed mood by increasing the severity or functional impairment. Severity and impairment tend to be positively correlated, but the former is a function of the "development, spread, and depth of dysfunction of the disease or disorder, while impairment is an outcome of the underlying disease in a given environment, concerning what people can do in terms of activities." (Ustun & Kennedy, 2009). Neither depression severity or impairment are clearly defined or operationalized in the DSM, even though clinically significant distress and impairment are part of the qualifying criteria, and an integral to the clinical judgment of severity (American Psychiatric Association, 1994, 2013). In the DSM, there are three levels of depression severity (mild, moderate, and severe) with or without psychotic features, but the concepts of severity and impairment are somewhat conflated:

> **Mild**: Few, if any, symptoms in excess of those required to make the diagnosis, and the symptoms result in only minor impairment of occupational functioning or in the usual social activities or relationships with others.
>
> **Moderate**: Symptoms or functional impairment between "mild" and "severe".

**Severe without psychotic features**: Several symptoms in excess of those required to make the diagnosis, and symptoms that markedly interfere with occupational functioning or the usual social activities or relationships with others.

**Severe with psychotic features**: Delusions or hallucinations.

(American Psychiatric Association, 1994).

By contrast, the WHO-ICD system avoids this complexity altogether by determining depression severity (mild, moderate, severe) based on number of symptoms alone, and making no mention of "impairment" or “disability” (World Health Organization, 1993). The WHO definition of disability encompasses functional domains such as learning and applying knowledge, general tasks and demands, communication, mobility, self-care, social functioning, and school/occupational functioning (Ustun & Kennedy, 2009).

Depression severity has been variously measured as the number of symptoms, intensity of symptoms, or in reference to suicide co-morbidity (Lux, Aggen, & Kendler, 2010). It may be an important indicator for the degree of psychiatric co-morbidity with other disorders, affect treatment outcomes, and predict depression recurrence (Fournier et al., 2010; Judd et al., 2000; Keller et al., 1992; Kirsch et al., 2008; Nemeroff, 2007; Shapiro et al., 1994). Within the cannabis-depression literature, depression severity has been studied as the sum of depression symptoms or a latent dimension using depression symptom scales. These studies of depression as a continuous outcome tend to be more consistent in finding a positive relationship with cannabis smoking (Fleming, Mason, Mazza, Abbott, & Catalano, 2008; Griffith-Lendering, Huijbregts, Mooijaart, Vollebergh, & Swaab, 2011; Groth & Morrison-Beedy, 2010; Horwood et al., 2012; Otten, Barker, Maughan, Arseneault, & Engels, 2010; Pahl, Brook, & Koppel, 2010; Repetto, Zimmerman, & Caldwell, 2008).

Functional impairment may be just as clinically relevant as severity measures. An estimated 59% of past 12 month cases of major depressive episode (MDE) rated their impairment severe or very severe within in a U.S. general population sample (Kessler et al., 2003). Co-morbidity was common among these MDE cases with severe impairment, with 24% having a co-morbid substance use disorder. Among adolescents (13-17 years) with major depression/dysthymia, about a third experienced serious impairment, which was defined as either moderate impairment in multiple areas (i.e., fears and anxieties that lead to gross avoidance behavior, episodes of aggression, or antisocial behavior), or severe impairment in one area (Kessler et al., 2012).

Few studies have reported on the relationship between cannabis smoking, depression, and functional impairment. In one study, cannabis smoking was part of a scale of risky behaviors that also included cigarette smoking, alcohol use, sexual intercourse, violence, and suicide (Flisher et al., 2000). Several correlates of risky behaviors were evaluated, including various stressors, individual resources (e.g., social competence, verbal intelligence, and parental monitoring), biological dispositions, and psychopathology (e.g., mood disorder, anxiety disorder, disruptive disorder, and functional impairment). Higher levels of risky behaviors were associated with having a mood disorder and greater functional impairment. However, the assessment of functional impairment was non-specific to any particular cause, and all risky behaviors were grouped together, hence it is unknown the degree cannabis smoking specifically contributed to the correlation with depression or functional impairment.

Another study focused specifically on co-morbidity between cannabis use disorders and mood disorders in the previous 12 months in a household sample of teens from the Houston, Texas metropolitan area (R. E. Roberts, Roberts, & Xing, 2007). In unadjusted models, teens

diagnosed with any cannabis use disorder had three times the odds of having a mood disorder. The researchers then examined those with a mood disorder *and* scored below the mean on the Child Global Assessment Scale (CGAS), a measure of functional impairment with lower scores indicating greater impairment. Cannabis abuse was associated with a seven-fold excess odds (95% CI: 2.2, 26.8), but no association was observed for teens with cannabis dependence. However, models that adjusted for alcohol and other drug use disorders produced either null or unstable estimates due to too little or no variation in the mood disorder/functional impairment outcome.

A more recent study of a clinical sample of youths seeking treatment for a primary mood or anxiety disorder found those with higher scores on a scale of alcohol, tobacco, and other drug use had higher levels of depression and more impairment (Osuch, Vingilis, Ross, Forster, & Summerhurst, 2013). However, in these studies it is unclear the degree to which cannabis smoking might be the causal influence, and whether the impairment experienced was due to depression or other sources.

One exception was a study of college students whose cannabis use trajectories were followed for seven years (Caldeira et al., 2012). Students whose cannabis use was characterized as early-decline, late-increase, college-peak, or chronic had more days of impairment due to emotions and higher depression scores than non-users or low-stable groups, adjusting for trajectories of alcohol and tobacco use. Research on this topic could be furthered by studying the relationship between cannabis smoking, depression, and functional impairment in general population samples as proposed in this dissertation.

## 2.7. The Blunt Smoking Phenomenon

Studies conducted primarily in the U.S. have reported a gradual increase in the rates of both cannabis use and dependence beginning in the 1990s and then remaining relatively stable throughout the 2000s (Compton, Grant, Colliver, Glantz, & Stinson, 2004; Gfroerer et al., 2002; Golub et al., 2005). Some researchers have suggested this recent resurgence of cannabis smoking is due to a higher THC content or more early-onset use (Compton et al., 2004). An alternate viewpoint proposes that youths born since 1970 are eschewing what some might describe as "hard" drugs, such as cocaine and heroin, in favor of consuming cannabis, particularly in the form of a 'blunt' (Golub & Johnson, 1999). A blunt is constructed from an inexpensive cigar by replacing the tobacco contents with cannabis. This method of cannabis delivery is contrasted by an American 'joint', in which cannabis is wrapped in cigarette paper. It should be noted that Europeans commonly mix tobacco and cannabis in a 'joint', which is also called a 'blowtje' in the Netherlands (Ream et al., 2006). 'Chasing', where smoking a joint or blunt is quickly followed by smoking a cigar or other tobacco product, may also be similar in terms of the mechanisms and consequences of tobacco-cannabis co-administration. Blunt smoking originated and gained popularity among New York City youths, especially African-American males connected to the emerging hip-hop music scene of early 1990s (Golub, Johnson, Dunlap, & Sifaneck, 2004).

Blunt smoking has become quite common in the U.S., with evidence of increasing prevalence over time, and shrinking subgroup differences. A school-based study of youths from grades 7-12 estimated the overall lifetime prevalence to be as high as 20% (Soldz, Huyser, & Dorsey, 2003), however, a more nationally representative sample of 12-17 year olds placed overall blunt smoking prevalence closer to 11% (Golub et al., 2005). Nearly half of all cannabis

users have smoked a blunt, but prevalence in some population subgroups may be as high as 80-90% with males, African-Americans, older youths, and those living in urban areas being over-represented (Golub et al., 2005; Substance Abuse and Mental Health Services Administration, 2007; Timberlake, 2013). Between 2000 and 2010, the overall prevalence of blunt smoking increased from 11% to 14%, with evidence that African-American cohorts persisted in their blunt use into adulthood, and younger cohorts of other race/ethnic subgroups catching up to African-American youths (Golub et al., 2005; Timberlake, 2013).

Public health researchers concerned about consequences of cannabis consumption, especially among youths and minority groups, should be particularly interested in the blunt phenomenon. Ethnographers report blunt smokers to be culturally distinct from other cannabis users, with unique practices, rituals, and terminology, which could have implications for targeting health messages and interventions (Dunlap, Johnson, Benoit, & Sifaneck, 2005; B. D. Johnson, Bardhi, Sifaneck, & Dunlap, 2006; Kelly, 2005; Sifaneck, Johnson, & Dunlap, 2005). A blunt a can hold greater quantity of cannabis than a joint, burn slower and longer, can be more easily passed around, and is more portable and disposable (Kelly, 2005; Mariani, Brooks, Haney, & Levin, 2011). Some blunt users (28%) reported adding other drugs to the blunt, including cocaine, heroin, or psychedelics (e.g. LSD, PCP, mescaline) (Soldz et al., 2003). When properly constructed, a passing observer might find a blunt to be indistinguishable in both appearance and smell to a non-cannabis cigar. Youths find this aspect of concealing their cannabis consumption, especially in more public areas, to be appealing (Sifaneck et al., 2005). In addition, the marketing of cigar 'flavors' (e.g., bubble gum, fruit flavors, vanilla) among brands popular for blunt use, and 'blunt wraps' (tobacco leaf paper), is attractive to youths, novice users, minorities, and women (Sifaneck et al., 2005). The nicotine content of blunts may be low, yet blunt smokers are

more likely to be nicotine dependent and may use tobacco cigarettes a higher rates (Timberlake, 2009). This could differentially expose blunt smokers to greater health risks associated with tobacco, which are well documented (US Department of Health and Human Services, 2004).

Another potential concern is whether blunt smoking might influence the experience and development of a cannabis use disorder (CUD). Nicotine and THC might interact pharmacologically to affect tolerance, withdrawal, and physiological responses (Valjent et al., 2002). For example, a pre-clinical study found that co-administration of nicotine and THC produced differential physiological effects (lower body temperature, locomotion, and pain sensitivity), slowed tolerance to these effects, and increased anxiety-like behaviors greater than the additive effect of each drug alone (Valjent et al., 2002). Cannabinoid CB1 and nicotinic receptors may play a role in neuromechanisms underpinning dependence and the reinforcing effects for both substances (Viveros, Marco, & File, 2006). A qualitative report observed that blunt smokers believed blunts to be habit-forming due to the nicotine, and not the cannabis content (Dunlap, Benoit, Sifaneck, & Johnson, 2006). Some researchers have proposed that alleviating the nicotine withdrawal produced from mixing tobacco and cannabis perpetuates their co-use (Burns, Ivers, Lindorff, & Clough, 2000; Van Beurden, Zask, Passey, & Kia, 2008). Social settings, rituals, and normative behaviors associated with blunt smoking might also serve to reinforce cannabis consumption (Dunlap et al., 2006, 2005, p. 2005; Kelly, 2005; Ream et al., 2006). While Dunlap et al. (2006) observed that group norms discouraged excessive blunt use or intoxication, it is not known whether blunt smoking promotes more frequent blunt or non-blunt cannabis use. Golub, Johnson, and Dunlap (2005) contend that the rise in rates of cannabis use during the 1990s was due to blunts. An epidemiologic study by Compton et al. (2004) reported

that the largest increases of cannabis use disorders during the 1990s occurred for African-Americans, although the authors did not differentiate between cannabis and blunt use.

Only two studies have investigated the relationship between blunt smoking and cannabis use disorders, or with symptoms of cannabis dependence. In one study, Ream et al. (2008) found that blunt smoking and 'chasing' cannabis with tobacco was uniquely associated with five out of seven cannabis problems: 'spent more time using than intended', 'neglected usual responsibilities', 'preoccupied with use', tolerance, and 'used to relieve negative affect' as compared to non-blunt smokers. No relationship was found for 'wanted to cut down but could not' or 'made psychological problems worse'. In a second study, Timberlake (2009) compared past month blunt smokers to never blunt smokers and found the former has around twice the odds of having cannabis use disorder in the past-year, adjusting for tobacco smoking and background characteristics. Never blunt smokers were compared to groups of other cannabis users based on how much past month level of blunt smoking exceeded past month level of cannabis use. Therefore, blunt smokers with relatively little blunt smoking that nevertheless exceeded cannabis use (e.g., two days of blunt smoking, but one day of cannabis use) may have been grouped with heavy blunt smokers (e.g., used blunts every day). Not surprisingly, there was little difference in the odds of CUDs among blunt using groups.

# CHAPTER 3. MATERIALS AND METHODS

Chapter 3 details the materials and methods for each of the four studies comprising this dissertation research project. Studies 1, 2, and 3 relied upon data gathered in the United States (US) National Surveys on Drug Use and Health (NSDUH). Therefore, the first section of the chapter (3.1) describes the study methodology these research projects have in common. Study 4 relied upon data gathered in the World Health Organization World Mental Health Survey Initiative (WHO-WMH). Details of this study are covered in section 3.2. The final section of this chapter (3.3) explains the analysis approach for each study individually.

## 3.1. The U.S. National Surveys on Drug Use and Health (NSDUH)

### 3.1.1. Study Background, Design, and Population

The NSDUH are a series of annual, cross-sectional surveys on the use of tobacco, alcohol, cannabis, and other drugs, along with mental health correlates and health care utilization (United States Department of Health and Humans Services, 2012). This series has been ongoing since the 1970s, with annual surveys since 1990. Previously titled the National Household Survey on Drug Abuse (NHSDA) and run by NIDA, the NSDUH is currently administered by the Substance Abuse and Mental Health Services Administration (SAMHSA), which is a department of the U.S. Department of Health and Human Services (DHHS). The NSDUH study population now is designated to include the non-institutionalized, civilian population of the U.S. aged 12 years and older. Approximately 65,000-69,000 persons were surveyed each year. Due to confidentiality concerns, only a subset of the total sample surveyed was made publically available by SAMHSA. This dissertation research used the publicly available data collected between 2004 and 2011 (Table 3.1.1). Overall response levels between 2004 and 2011 ranged

from 65% to 70%, as determined by the joint probability of completing the screening interview to roster eligible household participants, and completing the survey interview conditional on being selected to participate.

**Table 3.1.1.** U.S. National Surveys on Drug Use and Health, Overall Samples Sizes and Response Levels, 2004-2011.

| Survey Year | Sample Surveyed | Public Use Sample | Weighted Screening Response Rate | Weighted Interview Response Rate | Overall Response Level[a] |
|---|---|---|---|---|---|
| 2004 | 67,760 | 55,602 | 91% | 77% | 70% |
| 2005 | 68,308 | 55,905 | 91% | 76% | 69% |
| 2006 | 67,802 | 55,279 | 91% | 74% | 67% |
| 2007 | 67,870 | 55,435 | 89% | 74% | 66% |
| 2008 | 68,736 | 55,739 | 89% | 74% | 66% |
| 2009 | 68,700 | 55,772 | 89% | 76% | 67% |
| 2010 | 68,487 | 57,873 | 89% | 75% | 66% |
| 2011 | 70,109 | 58,397 | 87% | 74% | 65% |

[a]Response level = Screening response rate x Interview response rate
Source: U.S. Department of Health and Human Services. U.S. National Surveys on Drug Use and Health, Codebooks 2004-2011.

### 3.1.2. Sampling Approach

The sampling approach involved a multi-stage area probability sample design. The NSDUH is a nationally-representative household sample of U.S. residents, with sampling frames that included civilians living on military bases, residents of non-institutionalized group quarters (e.g., college dormitories and group homes), and dwellings for persons without a permanent residence (e.g., homeless shelters and hotel residents). Thus, the sampling frame excluded members of the active-duty military and persons living in institutionalized group quarters (e.g., hospitals, prisons, nursing homes, and treatment centers), which represented less than two percent of the population (United States Department of Health and Humans Services, 2012). The primary sampling unit (PSU) consisted of geographical State sampling regions (SSRs), and was

based on U.S. Census tracts aggregated to include a minimum number of dwelling units (DU) per SSR. Samples were drawn from each of the 50 U.S. States in addition to the District of Colombia. A smaller secondary sampling unit (SSU), composed of adjacent census blocks, was selected within the PSU in cases where the PSU greatly exceeded DU requirements. There was a 50% overlap in use of SSUs between successive survey years. Adolescents and young adults were oversampled in order to collect approximately the same number of respondents across three age groups: 12-17 years, 18-25 years, and 26 years or older.

### 3.1.3. Methodology, Confidentiality, and Human Subjects Protection

Trained field interviewers (FIs) conducted screening and survey interviews with designated respondents (DRs) using computer assisted interviewing (CAI) methods. Screening interviews with an adult resident identified all eligible persons within the DU (12 years or older), including their age, sex, race/ethnicity, and military status. FIs read the study description and received informed consent from both the screening respondent and DR(s). For DRs 12 to 17 years of age, FIs received verbal consent from a parent or guardian before approaching the minor for informed consent. Survey interviews were conducted using a combination of computer-assisted personal interviewing (CAPI) and audio computer-assisted self-interviewing (ACASI) methods. CAPI methods collected data on non-sensitive topics, while ACASI methods collected data on sensitive topics, such as drug use. This method benefited from increased confidentiality of responses and an increased level of honest reporting. Respondents received $30 after the interview in appreciation for their time.

All survey materials and procedures were approved by the cognizant institutional review board (IRB) for the protection of human subjects. To protect respondent confidentiality,

identification information elements (e.g., name and addresses) were not linked to respondent's interview data. Census tract, state, and other geographical information were also removed from the public use data. Post-interview statistical disclosure limitation methods identified records where the confluence of variables such as sex, age, race/ethnicity, and other responses might compromise confidentiality. In some cases, substitution of variables from a similar donor record was used. Random sub-sampling, in which random records were removed, also decreased the probability of identifying a record based upon responses. Values for some core demographic information such as sex, age, race/ethnicity, and income were imputed either through logical editing or statistical imputation. Unless noted otherwise in this dissertation, missing values on other variables were due to bad data, respondent non-response (i.e., left blank, refused to answer, or did not know the answer), or were not asked the question(s) due to logical skip patterns.

### 3.1.4. Reliability and Validity Studies

A reliability study using a subsample of respondents from the 2006 NSDUH sample was conducted five to 15 days after the initial survey by SAMHSA (Substance Abuse and Mental Health Services Administration, 2010). Cohen's kappa was one statistic used to measure consistency between initial and follow-up responses. Kappa values can be interpreted based on recommendations by Landis and Koch (1977): poor agreement for kappa less than 0.00; slight agreement for kappa of 0.00 to 0.20; fair agreement for kappa of 0.21 to 0.40; moderate agreement for kappa of 0.41 to 0.60; substantial agreement for kappa of 0.61 to 0.80; and almost perfect agreement for kappa of 0.81 to 1.00. Kappa estimates were 0.70 or better for lifetime drug use variables, 0.47 to 0.85 for age of first use (agreement within 1 year), and 0.60 or better for drug abuse and dependence measures among all respondents. Reliability for blunt smoking

measures (lifetime and past-year use) were 0.66 or greater. For major depressive episode (MDE) measures among adults 18 or older, kappa values for lifetime, past-year, and age of first depression were 0.67, 0.52, and 0.65, respectively. Corresponding values among adolescents 12-17 years were 0.66, 0.72, and 0.41.

A NHSDA validity study was performed in 2000-2001 among past month drug users (Harrison, Martin, Enev, & Harrington, 2007). Although not directly related to data used for this study, results may nevertheless be informative. A maximum of one person per household was selected and the study excluded residents of Alaska and Hawaii, Spanish-only speakers, and respondents older than 25 years of age (n = 4,465; participation and biological specimen response level: 74% and 89%, respectively). Urine and hair specimens were analyzed for the following drugs or metabolites: cotinine, (for tobacco), marijuana metabolite (delta-9-tetrahydrocannabinol carboxylic acid, carboxy-THC), cocaine metabolite (benzoylecgonine or BZE), amphetamines (amphetamine and methamphetamine), and opioids (codeine and morphine). Percent agreement between recent self-report measures and urinalysis showed strong agreement for tobacco (89%), cannabis (90%), and cocaine (98%). Sample sizes and positive urine tests were too small to draw conclusions for opiates and stimulants. Technical and statistical issues prevented the use of hair specimens in the study.

### 3.1.5. General Strengths and Limitations of the NSDUH Studies

Use of NSDUH data had a number of strengths compared to recent and prior epidemiologic studies of drug use behaviors. First, it is perhaps the largest survey of drug use behaviors to date. By comparison, sample sizes for the Epidemiologic Catchment Area (ECA) study, and the U.S. National Comorbidity Study – Replicate (NCS-R) had sample sizes of about

21,000 and 10,000, respectively. Large sample sizes helped produce statistically precise estimates, especially for behaviors or conditions that would be normally rare in community samples. Second, the NSDUH is ongoing and conducted annually. This allows researchers to produce timely and relevant estimates of drug behavior, and replicate their results relatively quickly using independent samples collected using nearly identical methods. Third, estimates from the NSDUH are more representative of the drug-using population compared to other similar ongoing surveys, such as the Monitoring the Future (MTF) and Youth Risk Behavioral Surveillance (YRBS) surveys. For example, the MTF study annually surveys only U.S. students in grades 8, 10, and 12, while the YRBS study samples U.S. students in grades 9-12 every other year (Centers for Disease Control and Prevention, 2012; Johnston, O'Malley, Bachman, & Schulenberg, 2012).

Despite these strengths, some limitations of the NSDUH must be considered. First, responses to questions about drug use behaviors were based on self-report, which may not be completely free of recall bias, reporting error, or dishonest response. The use of CAPI and ACASI methods mitigated some of these limitations, and the reliability study mentioned above attempted to quantify it. Second, these surveys were cross-sectional rather than longitudinal, and therefore this research was limited in its ability to make causal inferences when the temporal sequence between variables was ambiguous. Nevertheless, this research endeavored to take into account temporality by using age-of-onset information when available. Third, as mentioned above, these surveys do not target children (less than 12 years), active-duty military, and persons in institutionalized group quarters (such as prisons), and therefore results may not generalize to these populations.

3.1.6. Measurement of Key Study Variables

Several aspects of drug use behavior were measured for cannabis, blunts, tobacco cigarettes, alcohol, and other internationally regulated drugs (IRD). Relevant to this dissertation research were lifetime use, past-year use, past-month use, past-month and year frequency, features of problematic use, age of first drug use, and age of last drug use. Frequency of drug use in the past month or year was measured in relation to the number of drug-using days, rather than quantity (e.g., number of drinks or cannabis joints smoked). Frequency of past-month tobacco and blunt use was assessed, but not past-year frequency as with alcohol, cannabis, or other drugs. Questions pertaining to the cannabis and blunt use were asked in separate points in the interview, however, all questions about problematic cannabis use did not reference blunts. The variable "blunt smoking recency" was constructed from responses to lifetime, past-year, and past-month blunt use to have the following categories: a) never blunt smokers; b) used blunts at some point, but not within the past 12 months (i.e., prior use); c) used blunts sometime within the past-year, but not within the past month (i.e., past year); d) used blunts within the past month (i.e., past month). Variables referencing early-onset drug use were based on self-report age of first drug use and defined as having initiated the drug prior to age 18 years. Similarly, adult-onset was defined as started to use the drug at age 18 or older. Years of cannabis involvement was defined as the number of years from first to last use of cannabis.

Except for tobacco, items that measured problematic alcohol or cannabis use features were based on dependence and abuse criteria in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV; American Psychiatric Association, 1994). Questions were drug-specific, covered the respondent's past 12 month experience, and were asked only if the respondent had used alcohol or cannabis on more than five days in the past year (see Table 3.1.2

for list of features). Participants who used less than this amount were imputed to not have experienced the feature. Cannabis withdrawal was not measured, as it was not recognized as a clinical feature under the DSM-IV. Responses to each feature were coded as dichotomous.

**Table 3.1.2.** Features of cannabis/alcohol problems (CP/AP) based on diagnostic criteria from the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*.

| CP Variable | AP Variable | Description |
|---|---|---|
| CP1 | AP1 | Spent a great deal of time over a period of a month getting, using, or getting over the effects of [cannabis/alcohol]. |
| CP2 | AP2 | Used [cannabis/alcohol] more often than intended or was unable to keep set limits. |
| CP3 | AP3 | Needed to use [cannabis/alcohol] more than before to get desired effects or noticed that same amount of cannabis use had less effect than before. |
| CP4 | AP4 | Inability to cut down or stop using [cannabis/alcohol] every time tried or wanted to. |
| CP5 | AP5 | Continued to use [cannabis/alcohol] even though it was causing problems with emotions, nerves, mental health, or physical problems |
| CP6 | AP6 | Gave up or reduced involvement or participation in important activities due to [cannabis/alcohol]. |
| CP7 | AP7 | Serious problems at home, work, or school caused by using [cannabis/alcohol]. |
| CP8 | AP8 | Used [cannabis/alcohol] regularly and then did something that might have put you in physical danger. |
| CP9 | AP9 | [Cannabis/Alcohol] caused you to do things that repeatedly got you in trouble with the law. |
| CP10 | AP10 | Problems with family or friends caused by using [cannabis/alcohol] and continued to use cannabis even though you thought using [cannabis/alcohol] caused these problems. |
| NA | AP11 | Reported experiencing two or more alcohol withdrawal symptoms at the same time that lasted longer than a day after alcohol use was cut back or stopped. |

NA, Not Applicable.

Tobacco dependence (TD) was measured in relation to tobacco cigarette smoking and only among past month smokers. Table 3.1.3 shows TD assessed using 19 items from the Nicotine Dependence Syndrome Scale (NDSS) and one item from the Fagerstrom Test of

Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991; Shiffman, Waters, & Hickcox, 2004). The NDSS is a scale designed to measure five aspects of dependence: (1) Smoking drive; (2) Nicotine tolerance; (3) Continuous smoking; (4) Behavioral priority; (5) Stereotypy. With one exception, responses were coded as 1 (not at all true), 2 (sometimes true), 3 (moderately true), 4 (very true), and 5 (extremely true). One item screened respondents about whether they had friends who smoked (TD6; yes vs. no) before being asked about whether they choose to be around friends who smoke (TD7). Responses from TD6 were incorporated into TD7, such that respondents who said they did not have friends who smoked were given the lowest value for TD7. Non-smokers or those who did not smoke in the past month were imputed to have either the lowest value (0) or highest value (6) depending on whether higher or lower values indicated more or less of the TD trait since some items were reverse coded. One item from the FTND asked about the length of time elapsed from waking in the morning until the first cigarette (within 5 minutes, 6-30 minutes, 31-60 minutes, and more than 60 minutes).

**Table 3.1.3.** Tobacco Dependence (TD) items based on Nicotine Dependence Syndrome Scale and Fagerstrom Test of Nicotine Dependence.

| Variable | Description |
|---|---|
| TD1 | Need to smoke to feel less irritable |
| TD2 | Start to crave cigarettes when don't smoke for few hours |
| TD3 | Craving of cigarettes like strong force can't control |
| TD4 | Feel a sense of control over your smoking |
| TD5 | Tend to avoid places that don't allow smoking |
| TD6 | Have friends who do not smoke cigarettes (yes/no) |
| TD7 | Choose not to be around friends who don't smoke |
| TD8 | Rather not travel by airplane because no smoking |
| TD9 | Sometimes worry that you will run out of cigarettes |
| TD10 | Smoke cigarettes fairly regularly throughout the day |
| TD11 | Smoke same amount on weekends as on weekdays |
| TD12 | Smoke same number of cigarettes from day to day |
| TD13 | Number of cigarettes smoke per day often changes |
| TD14 | Have many cigarettes in an hour, then no cigarettes until hours later |
| TD15 | # of cigarettes smoke per day influenced by other things |
| TD16 | Smoking not affected by other things |
| TD17 | Amount of smoking has increased since started smoking |
| TD18 | Need to smoke a lot more to be satisfied |
| TD19 | Smoke much more now before feel anything |
| TD20 | How soon after waking do you have your first cigarette? |

Depression was measured via a modified version of the World Mental Health Composite International Diagnostic Interview (WMH-CIDI), adapted from the NCS-R (Center for Behavioral Health and Statistics and Quality, 2012). A lifetime occurrence of a major depressive episode (MDE) was based on DSM-IV diagnostic criteria and required at least five or more clinical features that occurred every day, or nearly every day over a two-week or more time period, and where at least one feature was either (1) depressed mood, or (2) loss of interest or pleasure in most activities (i.e., anhedonia). Additional features included (3) significant changes in appetite or weight not accounted for by sickness, growth, pregnancy, or dieting, (4) insomnia or hypersomnia, (5) psychomotor agitation or retardation, (6) fatigue or loss of energy, (7)

feelings of worthlessness, (8) difficulty concentrating, thinking, or making decisions, and (9) recurrent thoughts of death or suicide (American Psychiatric Association, 1994). Respondents were asked these nine clinical features in relation to a period of time in their life when their mood was the worst, or if they could not recall the worst time, then their most recent episode. No exclusions were made due to bereavement, drug-induced depression, or diagnostic hierarchies. Therefore, there is a slight distinction between MDE defined within this research and that in the DSM.

This dissertation makes a further distinction between a MDE as just described and a depression spell. Those who qualified as a case of a MDE were also asked about when they first experienced a sustained spell of depressed mood or anhedonia that occurred most of the day, nearly every day for at least two-weeks or longer and had some of the same problems just described. They were further asked whether such a depression spell occurred in the past 12 months. Therefore, depression outcomes referring to the first or past-year occurrence of depression will be defined as depression spells, rather than a MDE. Using this information, respondents could be grouped into three categories based on lifetime depression status: 1) Never experienced a lifetime MDE; 2) "Prior depression" made up of those who had a lifetime MDE experience, but did not have a depression spell in the past 12 months; 3) "Past-year depression spell" consisting of those who experienced depression in the past 12 months.

Functional impairment attributed to depression was measured using the Sheehan Disability Scale (SDS), a short measure of global functional impairment related to mental health (Leon, Olfson, Portera, Farber, & Sheehan, 1997; Sheehan, Harnett-Sheehan, & Raj, 1996). The SDS was developed to measure impairment across three inter-related life domains: work/school, family/home life, and social life. The NSDUH used a modified version of the SDS, measuring

four domains for adults: (1) home management; (2) work; (3) close relationships; (4) social life. Due to difference in life roles, adolescents were asked about their degree of impairment with (1) chores, (2) school, (3) family, and (4) social life. In the analysis, categories of home management and chores were considered the same category when pooling data from adolescents and adults, as was work and school. SDS items were measured in relation to the time in the past 12 months when their mood was most severe, and rate the degree to which their depressed mood interfered in each life domain. Responses were measured via an analog scale from 0-10: 0 (no impairment), 1-3 (mild), 4-6 (moderate), 7-9 (severe), and 10 (very severe). For those who answered one or more SDS item of this series, an additional item asked about the number of days in the past year they were unable to carry out daily activities due to depressed mood, (range 0-365).

Conceptual models considered the influence of time-invariant background covariates such as sex, age, and race or ethnicity. Race or ethnic categories were defined with regards to standard U.S. census groups: White, Black or African American, Native American or Alaskan Native, Pacific Islander or Native Hawaiian, Asian, Hispanic, or more than one race. In most cases it was not possible to produce statistically precise estimates for ethnic/racial subgroups with relatively small sample sizes (e.g., Native American or Alaskan Native), nor was producing such estimates an aim of this dissertation. Thus, the main categories of White, Black/African-American, and Hispanic were retained, while all other groups were categorized as "Other". Additional background characteristics of interest were total family income (<$20K, $20K-$49,999, $50K-$74,999, and ≥$75K), and either county metropolitan type (large, small, non-metro) or population density. Population density was measured in relation to U.S. Census core-based statistical areas (CBSA).

### 3.1.7. Missing Data and Imputation

Respondents were excluded from analysis when missing on the outcome or variables used to define the analytical sample. Additional specific exclusion criteria were detailed in the analysis plan for each study below. Missing data on exposure variables were either logically imputed, dropped from analysis, or carried along in analyses under a 'missing' category as indicated in the description of the analyses. The public use data files provided by SAMHDA imputed missing data for core background variables (e.g., sex and race), income, lifetime drug use, and age-of-onset. These missing values that could not be logically imputed were imputed using a procedure called predictive mean neighborhood (PMN) imputation, which was a combination of model-assisted and nearest neighbor hot-deck imputation methods (United States Department of Health and Humans Services, 2012).

## 3.2. The WHO World Mental Health Surveys Initiative

### 3.2.1. Study Design and Sampling Procedures

Data for Study 4 come from the World Health Organization World Mental Health Surveys Initiative (WHO-WMHSI), the largest collaboration of coordinated, cross-national epidemiologic surveys of mental health disorders and treatment to date. Fourteen countries were included in this study, which collected data on cannabis use and the opportunity to use drugs (Table 3.2.1). Data from the Ukraine and South Africa could not be included because questions about drug opportunity were not asked. Additionally, data collected as part of the European Study Of The Epidemiology Of Mental Disorders (ESEMeD) had to be excluded due to a programming error that thwarted collection of data on problematic drug use features. Most studies were designed to include persons 18 years or older in the study population, with

exception of New Zealand (age 16+), Japan (20+), and Israel (21+). The sampling approach involved a multi-stage area probability sampling design to produce nationally or regionally representative samples. The first stage of sampling consisted of units analogous to counties or municipalities. The second stage sampling procedure targeted neighborhoods, towns, or other equivalent geographical clustering. Response levels varied from 51% (Japan) to 95% (Iraq). To reduce respondent burden, some sites administered core survey components to the entire sample (Part 1 sample), and then selected a subsample for interview of non-core components (Part 2 sample). Selection into the Part 2 sample was determined by screening criteria for any mental disorder and further enriched with a random 25% of remaining respondents. Only respondents interviewed about drug use provided information for this dissertation study. Table 3.2.1 reports the resulting sample size, and which part of the sample was administered the drug use interview module (Part 1 or Part 2).

**Table 3.2.1.** Sample Sizes and Study Characteristics of the WHO World Mental Health Surveys.

| Region/Country | Survey[a] | Survey Years | Response Level % | Ages | Sample Size | Sample Part Used |
|---|---|---|---|---|---|---|
| **Americas** | | | | | | |
| Brazil | SPM | 2004-6 | 81 | 18+ | 5,037 | Part 1 |
| Colombia | NSMH | 2003 | 88 | 18-65 | 4,426 | Part 1 |
| Mexico | M-NCS | 2001-2 | 77 | 18-65 | 5,782 | Part 1 |
| United States | NCS-R | 2002-3 | 71 | 18+ | 5,692 | Part 2 |
| **Europe** | | | | | | |
| Bulgaria | NSHS | 2003-6 | 72 | 18+ | 2,233 | Part 2 |
| Northern Ireland | NIMHS | 2004-8 | 68 | 18+ | 1,986 | Part 2 |
| Romania | RMHS | 2005-6 | 71 | 18+ | 2,357 | Part 1 |
| **Africa and Middle East** | | | | | | |
| Iraq | IMHS | 2006-7 | 95 | 18+ | 4,332 | Part 1 |
| Israel | NHS | 2003-4 | 73 | 21+ | 4,859 | Part 1 |
| Lebanon | LEBANON | 2002-3 | 70 | 18+ | 1,031 | Part 2 |
| Nigeria | NSMHW | 2002-4 | 79 | 18+ | 2,143 | Part 2 |
| **Western Pacific** | | | | | | |
| Japan | WMHJ | 2002-3 | 51 | 20+ | 1,305 | Part 2 |
| China | B-WMH, S-WMH | 2002-3 | 75 | 18-70 | 1,628 | Part 2 |
| New Zealand | NZMHS | 2003-4 | 73 | 16+ | 12,992 | Part 1 |

[a] SPM (Sao Paulo Megacity); NSMH (The Colombian National Study of Mental Health); M-NCS (The Mexico National Comorbidity Survey); NCS-R (The U.S. National Comorbidity Survey Replication); NSHS (Bulgaria National Survey of Health and Stress); NIMHS (Northern Ireland Mental Health Survey); RMHS (Romania Mental health Survey); IMHS (Iraq Mental Health Survey); NHS (Israel National Health Survey); LEBANON (Lebanese Evaluation of the Burden of Ailments and Needs Of the Nation); NSMHW (The Nigerian Survey of Mental Health and Wellbeing); WMHJ 2002-2003 (World Mental Health Japan Survey); B-WMH (The Beijing World Mental Health survey); S-WMH (The Shanghai World Mental Health Survey); NSMHWB (National Survey of Mental Health and Wellbeing); NZMHS (New Zealand Mental Health Survey)

### 3.2.2. Data Collection and Measurement of Psychiatric Disorders

Trained interviewers conducted face-to-face assessments using the World Mental Health Composite International Diagnostic Interview (WMH-CIDI), a fully structured diagnostic interview based on the WHO-CIDI (Kessler & Ustun, 2008). Consistent interviewer training, study materials, quality control, and standardized translation procedures were used across

surveys to minimize between site variations. Diagnostic measurements of mental, drug, and behavioral disorders were based on definitions and criteria from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV; American Psychiatric Association, 1994) and the *International Classification of Mental and Behavioral Disorders* (ICD; World Health Organization, 1993).

### 3.2.3. Protection of Human Subjects

Each participating country had their study protocols reviewed and approved by either a human subjects review board or ethics committee for the protection of human subjects (Kessler & Ustun, 2008). At all WMH sites, interviewers were required to read a statement of voluntary consent. However, sites varied in the method used to obtain consent depending on the literacy, culture, traditions, and norms of the country. Some countries required written consent of the participant, while other countries allowed for oral consent documented by the interviewer.

### 3.2.4. Measurement of Key Study Variables

Respondents was asked about lifetime history of use and age at which they first used the following drug sub-types: 1) alcohol; 2) cannabis; 3) cocaine; 4) extra-medical prescription drugs (e.g., analgesics, stimulants, and sedatives); 5) a catch-all category of 'other' drugs including heroin, LSD, ecstasy, etc. Tobacco cigarette smoking was measured in relation to current status at time of interview with the following categories: 1) Never smoked or smoked 'a few times'; 2) Ex-smoker; 3) Current smoker. Respondents were also asked separately about their first opportunity to use alcohol or drugs:

> The next questions are about the first time you had an opportunity to use [alcohol/drugs], whether or not you used them. By "an opportunity to use" I mean someone either offered you [alcohol/drugs], or you were present when others were using and you could have used if you wanted to. Please do not include times when a health care provider may have offered you free samples. Thinking back over your entire lifetime, about how old were you the very first time you had an opportunity to use [alcohol/drugs]?

The variable time to cannabis onset (TCO) was constructed by subtracting the value for age of first cannabis use from age of first drug opportunity.

Lifetime history of cannabis or alcohol dependence (CD/AD) were diagnosed (present vs. not present) based on the self-report experiences of clinical features from the DSM-IV and ICD-10 (see Table 2.4.1 from Chapter 2). Questions about AD features were alcohol-specific, but questions concerning dependence features for cannabis were not drug-specific *per se*, so this research restricted the analytical sample to respondents who had only used cannabis and no other IRD in their lifetime (i.e., 'cannabis-only'). Therefore, the experience of dependence features could be reasonably attributed to their cannabis use. In order to be asked questions about AD features, respondents had to have consumed more than once per month during the period of their life when they drank the most. For a few WMH survey sites, respondents first had to indicate the presence of at least one maladaptive drug problem in their lifetime prior to being asked questions about dependence (see Table 2.4.2 from Chapter 2). All problematic cannabis or alcohol drug features were coded as binary response variables (present vs. not present), and are listed with labels for each variable below (Table 3.2.2).

This research considered a number of covariates that might influence both time to cannabis onset and the experience of cannabis dependence or problems. These included sex, age, income (low, low-average, and above average), education (less than secondary vs. secondary finished), employment (working vs. not working), marital status (never married, previously married, and married/cohabiting), parent's highest level of education (primary or less, secondary, tertiary), and cumulative incidence of a major depressive episode up to the date of assessment (MDE).

**Table 3.2.2.** Features of cannabis/alcohol problems based on criteria from the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* and the *WHO International Classification of Diseases, 10th Revision*.

| Cannabis Variables | Alcohol Variables | Description |
|---|---|---|
| CP0 | AP0 | Strong desire to use |
| CP1 | AP1 | Spent a great deal of time getting or using |
| CP2 | AP2 | Used more often than intended |
| CP3 | AP3 | Experienced tolerance |
| CP4 | AP4 | Had difficulty cutting down when wanted to |
| CP5 | AP5 | Continued to use despite emotional or physical problems |
| CP6 | AP6 | Gave up important activities due to use |
| CP7 | AP7 | Serious problems home, work, or school |
| CP8 | AP8 | Hazardous use |
| CP9 | AP9 | Legal problems |
| CP10 | AP10 | Continued despite problems with family or friends |
| CP11 | AP11 | Experienced withdrawal |

### 3.3. Analysis Plan

3.3.1. Study 1: Early-Onset Cannabis Smoking and Depression Spells.

**AIM 1.** Estimate the degree to which early-onset (onset ≤ 17 years) and adult-onset (18+ years) cannabis smoking are associated with a later first onset of a depression spell in adulthood, within a conceptual model that accounts for time-invariant characteristics of sex, age, and race/ethnicity, and variation in tobacco and alcohol use.

Data for Study 1 came from the 2005-2009 NSDUH (n=278,130). The following groups were excluded from analysis: 1) Respondents 12-17 years who were not observed for the entire period of risk for starting to use cannabis (n=90,266); 2) Respondents whose first depression spell occurred before adulthood (n=11,229); 3) Invalid or otherwise missing data on depression status or age of first onset (n=2,265); 4) Cases whose cannabis onset occurred after their depression spell onset, in violation of an assumption that cannabis smoking must precede depression onset to be considered a viable causal factor (n=595). Thus, the analytical sample consisted of 173,775 adults. Early-onset cannabis use was defined as a dichotomous variable, which compared respondents whose age of cannabis onset was equal or less than 17, with those whose age of cannabis onset was later, or who had not used cannabis by the time of interview.

As described elsewhere (Anthony, 2004; http://www.epi.msu.edu/janthony/, last accessed 28 April 2014), the plan for data analysis was organized in relation to a now-standard "explore, analyze, explore" cycle. The first cycle involved exploratory steps such as histogram plots and other exploratory data analyses to shed light on the underlying distributions of the response variable and each covariate of interest. In this work, study estimates' precision is emphasized; the focus is on 95% confidence intervals. P-values are presented as an aid to interpretation. In the

initial analysis step, the author performed a series of logistic regressions, with occurrence of depression spell expressed as a function of cannabis onset timing, elapsed time of cannabis involvement, tobacco cigarette onset, and alcohol onset to produce unadjusted odds ratio (OR) estimates. All analyses took into account sampling weights and the complex sample structure for variance estimation purposes. In a subsequent analytical step, the statistical approach involved constructing a multivariable model that included all previously listed covariates plus adjustment for sex, age, race/ethnicity, and survey year. Our final exploratory analytical step consisted of probing the degree to which the early-onset cannabis estimate varied when introducing other covariates of interest into the model, but whose inclusion might otherwise violate the causal assumptions of the model. The first approach, called Add-One-In (AOI) analysis, consisted of estimating the EOCU-depression relationship with one additional covariate added to the previous multivariable model, removing the added covariate, and then re-estimating using a different covariate. This process was repeated for each covariate of interest. The second approach evaluated a statistical model that included all covariates together, and then used a backwards elimination procedure to reduce the number of covariates based upon having an overall p-value greater than 0.2. This backwards elimination method of model building has been recommended by others (Hosmer & Lemeshow, 2000; Royston & Sauerbrei, 2008). A leave-one-out (LOO) approach was used where by one covariate was left out of the multivariable model in order to see how sensitive the overall estimates were to the influence of any one particular covariate. Potential multicollinearity was evaluated using Spearman rank order correlations.

3.3.2. Study 2: Cannabis Problems and Functional Impairment Attributed to Recently Active Depression Spells.

**AIM 2.** Estimate the degree to which the level of cannabis problems is associated with the functional impairment attributed to depression in recently active cases, while accounting for differences in background characteristics, tobacco and alcohol use, and other relevant covariates.

Study 2 is based on NSDUH data collected from 2009-2011 (n=172,042). The analytical sample was restricted to respondents 12 years and older who experienced a depression spell within the past 12 months (n=13,743). Contingency tables were used to examine the distribution of the total sample and lifetime depression status (no depression, prior depression, and recently active depression spell) by relevant background characteristics (sex, age, race/ethnicity, income, and county metro). Next, SDS items were summarized using descriptive statistics and histogram plots were used to characterize their distribution.

Factor analysis was used to fit a hypothesized unidimensional latent trait of functional impairment (IMPAIR) using the five SDS items (Figure 3.1.1). In these figures, latent factors were represented by circles or ovals, and observed variables were represented by boxes. Hypothesized causal relationships between factors and/or observers variables are represented by directed arrows. Curved double-sided arrows indicated correlations. Prior literature indicated a single latent factor for the SDS, so no exploratory factor analysis (EFA) was performed (Arbuckle et al., 2009; Leon et al., 1997; Leon, Shear, Portera, & Klerman, 1992). A latent measurement model of two or more factors would likely have been under-identified given only five items in the scale. Factor analysis is based on the following equation:

$$\begin{bmatrix} x_1 \\ x_2 \\ x_p \end{bmatrix} = \begin{bmatrix} \lambda_{11} \\ \lambda_{21} \\ \lambda_{ij} \end{bmatrix} [f_j] + \begin{bmatrix} \varepsilon_1 \\ \varepsilon_2 \\ \varepsilon_p \end{bmatrix}$$, which is summarized by

$$\underline{x} = \Lambda \underline{f} + \underline{\varepsilon}$$

Where $\underline{x}$ is a $p$ x 1 vector of $p$ observed or manifest variables, $\Lambda = [\Lambda_{ij}]$ is a $p$ x $m$ matrix of factor loadings , $\underline{f}$ is the $m$ x 1 vector of factors, and $\underline{\varepsilon}$ is the $p$ x 1 vector of error terms assumed to be uncorrelated among themselves and with factors in $\underline{f}$. Factor analysis was similarly used to summarize hypothesized unidimensional latent traits for cannabis problems (CP), alcohol problems (AP), and tobacco dependence (TD) (see Figures 3.3.2, 3.3.3, and 3.3.4, respectively). EFA was not conducted on CP items for this study, but it was performed in Study 3. Comparative fit index (CFI), Tucker-Lewis Index (TLI), and root mean error of approximation (RMSEA) values were used to assess model fit. In this research, values for CFI and TFI $\geq 0.95$, and RMSEA $\leq 0.06$ were indicative of an excellent fit to the data (Browne, Cudeck, Bollen, & Long, 1993; Hu & Bentler, 1999). Modification indices (MI) were used to explore how the measurement models could be improved in case model fit was not adequate. MIs are an approximate measure of improvement (drop) in the chi-square value that would be gained if certain model parameters were not assumed to be constrained (Raykov & Marcoulides, 2008). Model re-specification would push analysis into exploratory mode, and the decision to change parameter constraints were based on both MIs and plausible substantive theory.

The association between latent traits of cannabis problems and impairment was estimated in a series of structural equation models (SEMs). The initial SEM estimated the unadjusted association between CP and IMPAIR. Subsequent SEMs added paths for hypothesized direct and indirect effects for sex, age, and race/ethnicity variables. Finally, latent traits for AP and TD were added (Figure 3.3.5). Post-estimation exploratory analyses compared estimates under

different measurement model assumptions for impairment, and then tested whether conclusions might differ after excluding respondents whose cannabis onset did not preceded onset of the first depression spell (i.e., using age-of-onset data to temporally constrain the hypothesized causal sequence). All models accounted for sample probability weights and the complex survey design. Initial analyses were done using Stata 12, but factor analyses and structural equation models were estimated using Mplus version 7 (Muthén & Muthén, 2012; StataCorp, 2011).

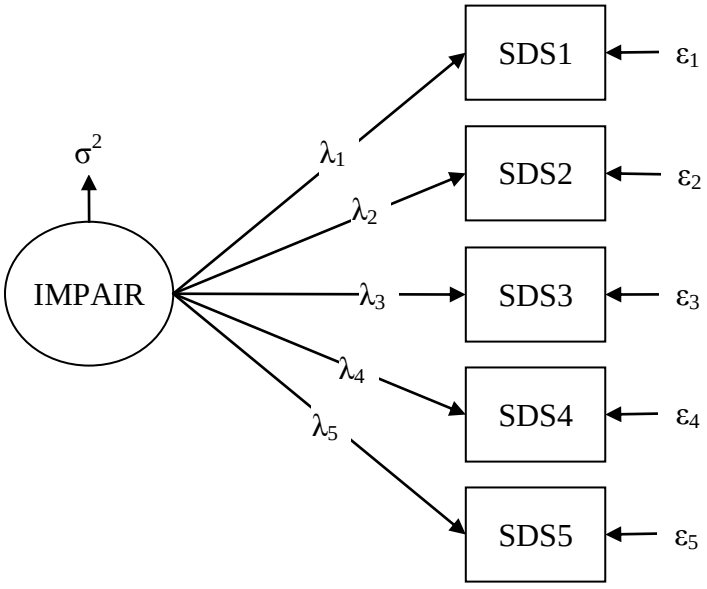



**Figure 3.3.1.** Hypothesized latent structure of functional impairment attributed to depression (IMPAIR).

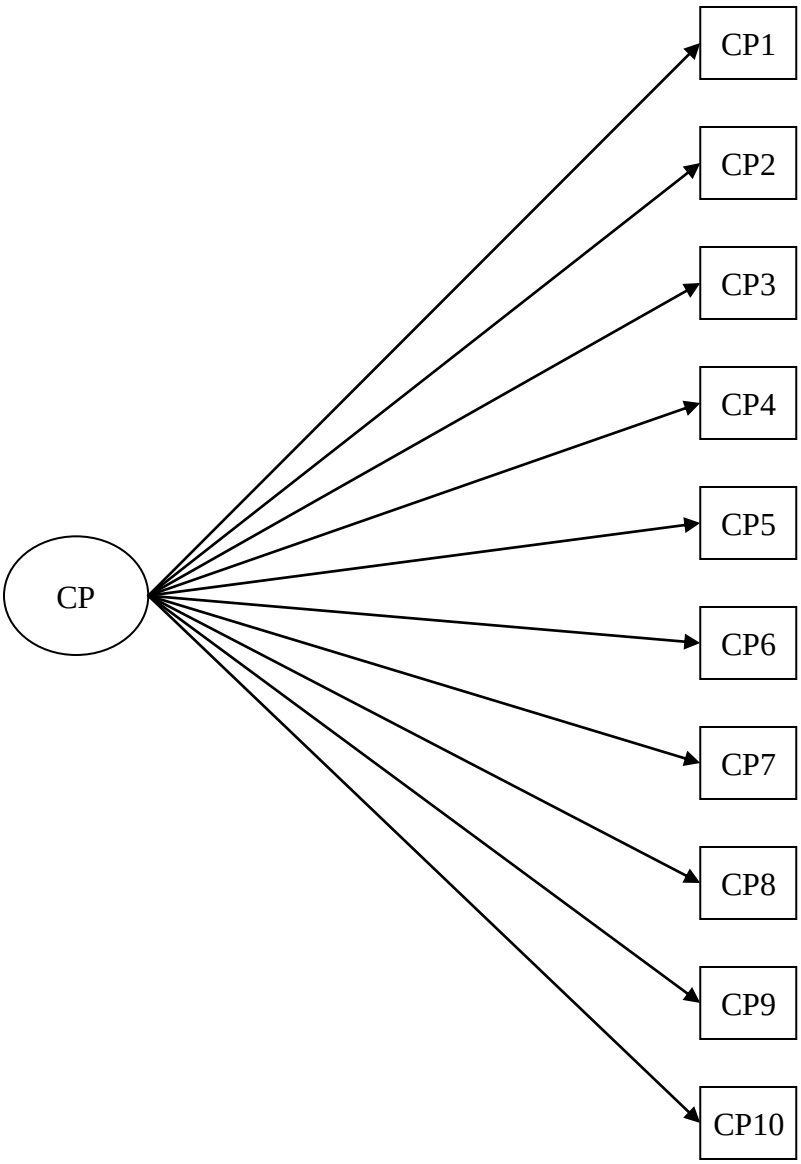



**Figure 3.3.2.** Hypothesized latent structure of cannabis problems (CP).

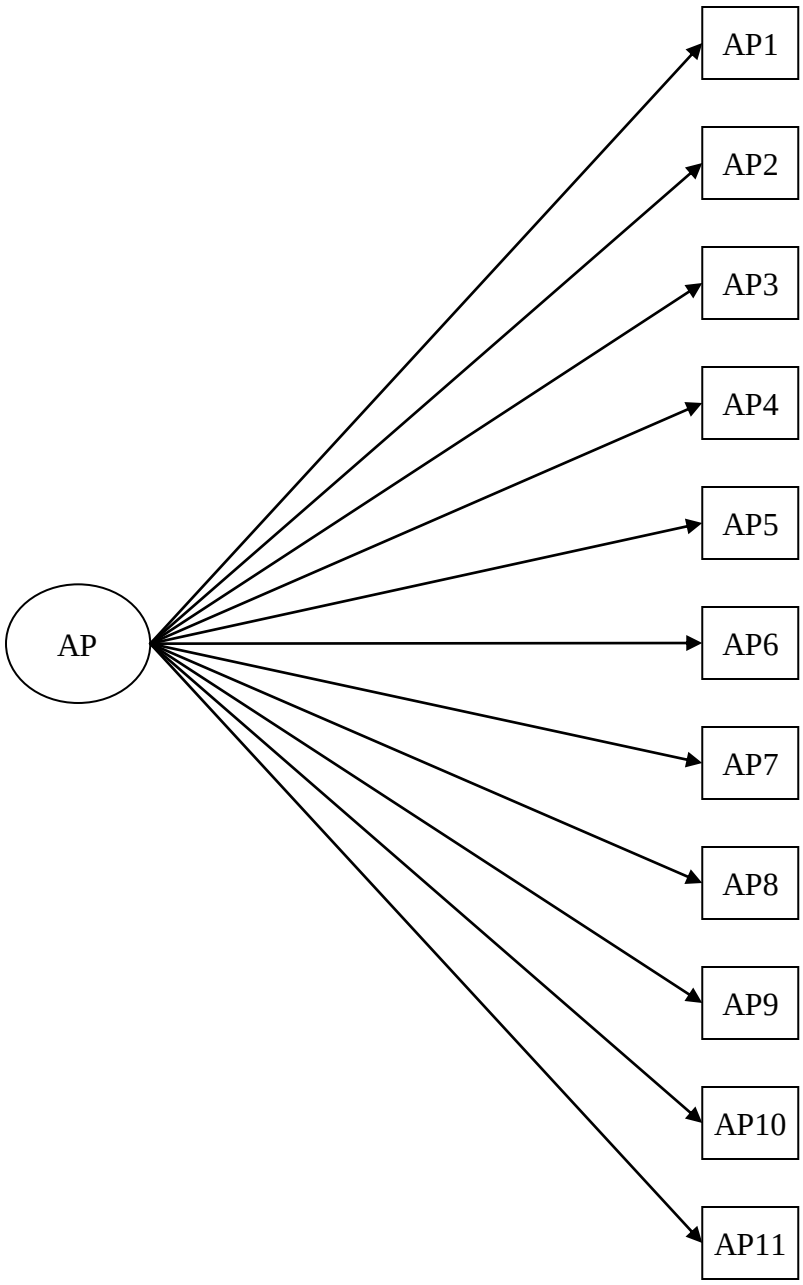



**Figure 3.3.3.** Hypothesized latent structure of alcohol problems (AP).

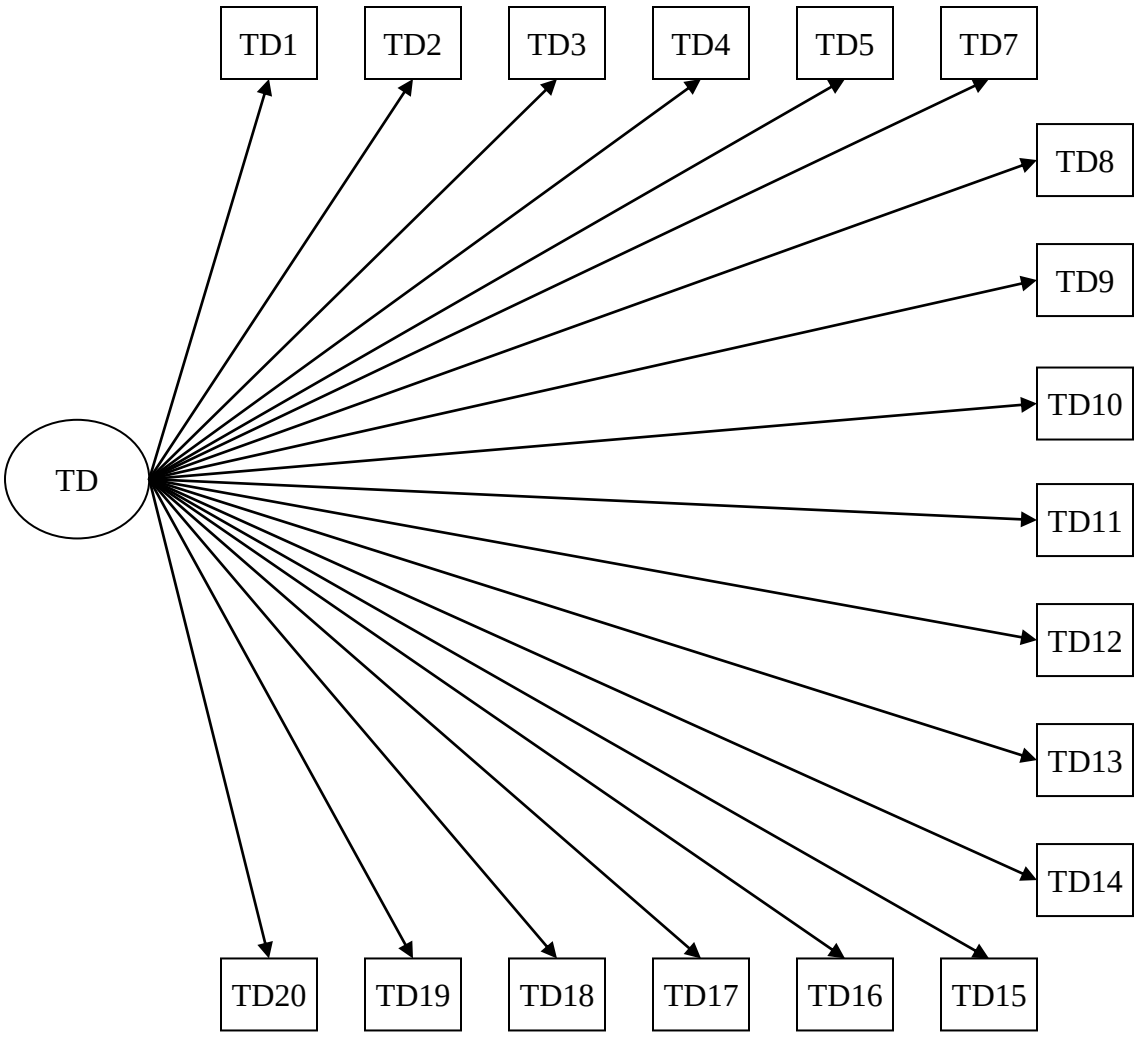



**Figure 3.3.4.** Hypothesized latent structure of tobacco dependence (TD).

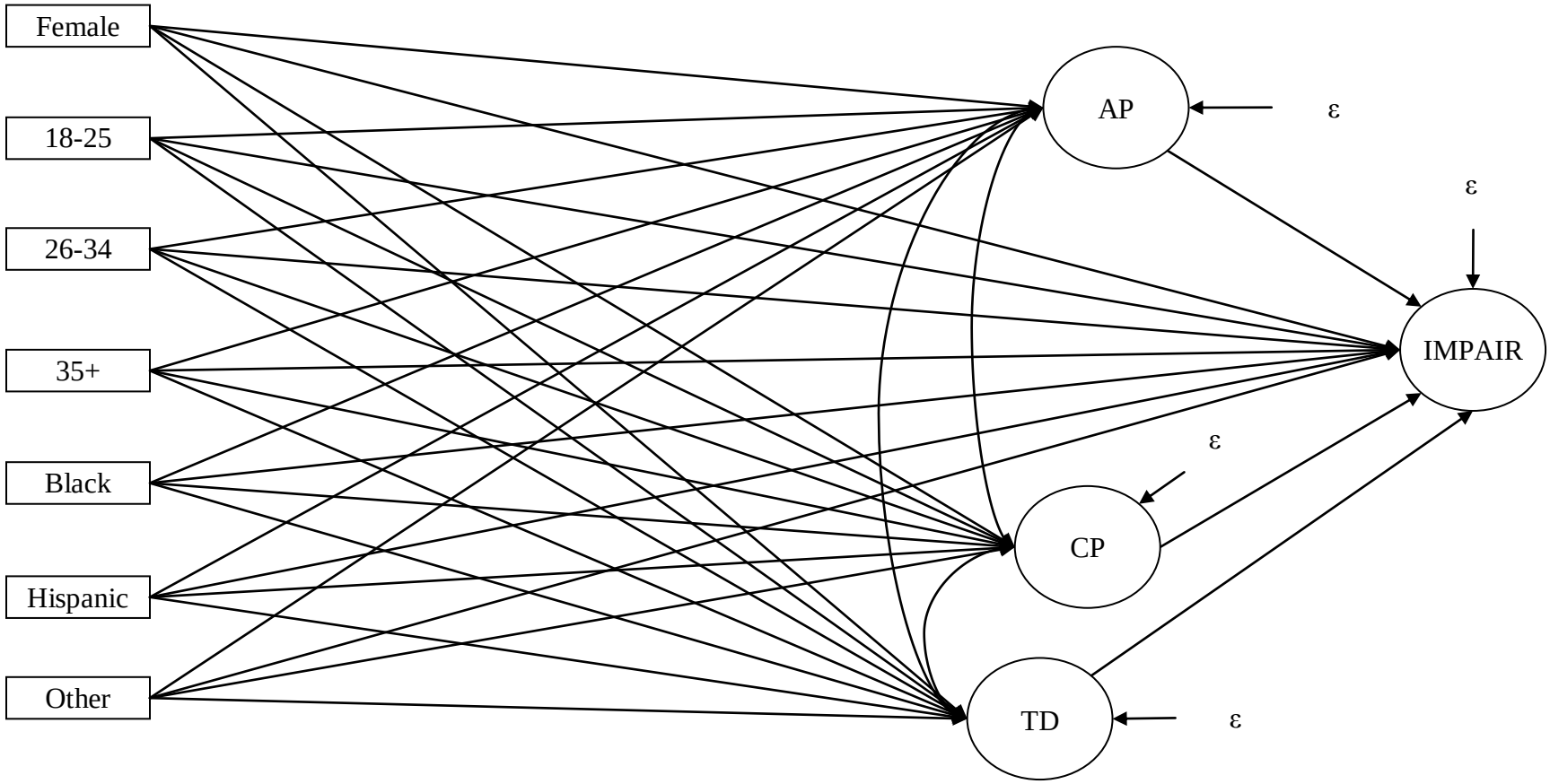



**Figure 3.3.5.** Model of relationships between functional impairment attributed to depression (IMPAIR) and cannabis problems (CP), alcohol problems (AP), tobacco dependence (TD), and background characteristics.

3.3.3. Study 3: Cannabis Problems and History of Blunt Smoking.

**AIM 3.** Estimate the degree to which a history cannabis 'blunt' smoking is associated with the level of cannabis problems experienced, within a conceptual model adjusting for the influence of sex, age, race/ethnicity, and other potential time-invariant covariates.

Data for Study 3 came from the NSDUH collected from 2004 to 2011 (n=450,002). Sample characteristics (i.e., sex, age, race/ethnicity, and population density) were compared between the total NSDUH sample and the analytical sample (n=77,047). The analytical sample consisted of respondents 12 years or older, had used cannabis in the past 12 months from the date of interview, and were assessed for problematic cannabis use. In the first phase of analysis, the weighted population prevalence of blunt smoking (i.e., ever, past-year, and past-month use) was estimated across survey years in order to characterize both the extent of blunt use in the population and its potential variation over time. Next, the prevalence of individual cannabis problems items were compared between non-blunt users and those who had used in their lifetime and within the past year.

In the second phase, exploratory factor analysis (EFA) was conducted using the ten features of cannabis problems (CP) from a random half-split sample of 2004 NSDUH data (n=3,534). Analysis used a weighted least squares mean variance (WLSMV) estimator and geomin oblique rotation. A scree plot of eigenvalues (EV) helped to evaluate the number of factors present. Confirmatory factor analysis (CFA) then was used to compare a single latent factor model of CP items versus a hypothesized model where CP1-CP6 items loaded on a cannabis dependence factor (DEPEND) and CP7-CP10 items loaded on a factor of socially maladaptive or hazardous cannabis use factor (HARM) (see Figures 3.3.2 above for the single

factor model, and Figure 3.3.6 below for the two-factor model). The second half-split sample of 2004 NSDUH data was used for this CFA analysis (n=3,520). Results from the EFA and CFA were used to inform the factor structure of cannabis problems used for later analysis. CFA was also conducted on alcohol problems (AP) and tobacco dependence (TD), with the assumption of a single underlying factor for each as depicted in Study 2 (see Figures 3.3.3 and 3.3.4, respectively).

In the third analysis phase, the association between level of cannabis problems and recency of blunt smoking was estimated by regressing CP factor scores on dummy coded indicators of blunt smoking recency, with never blunt smokers as the reference group (Figure 3.3.7). Subsequent SEMs first added observed covariates for sex, age, race/ethnicity, and population density, and then finally included latent factors for alcohol problems (AP) and tobacco dependence (TD), allowing for factor correlations between the three latent factors (Figure 3.6.8). Exploratory analysis investigated whether frequency of past-month blunt smoking was associated with CP in a model similar to the one depicted in Figure 3.6.7. All analyses took into account sample probability weights and the complex survey design. Initial analyses were carried out using Stata 12, but all EFA, CFA, and SEM analyses were conducted in Mplus version 7 (Muthén & Muthén, 2012; StataCorp, 2011).

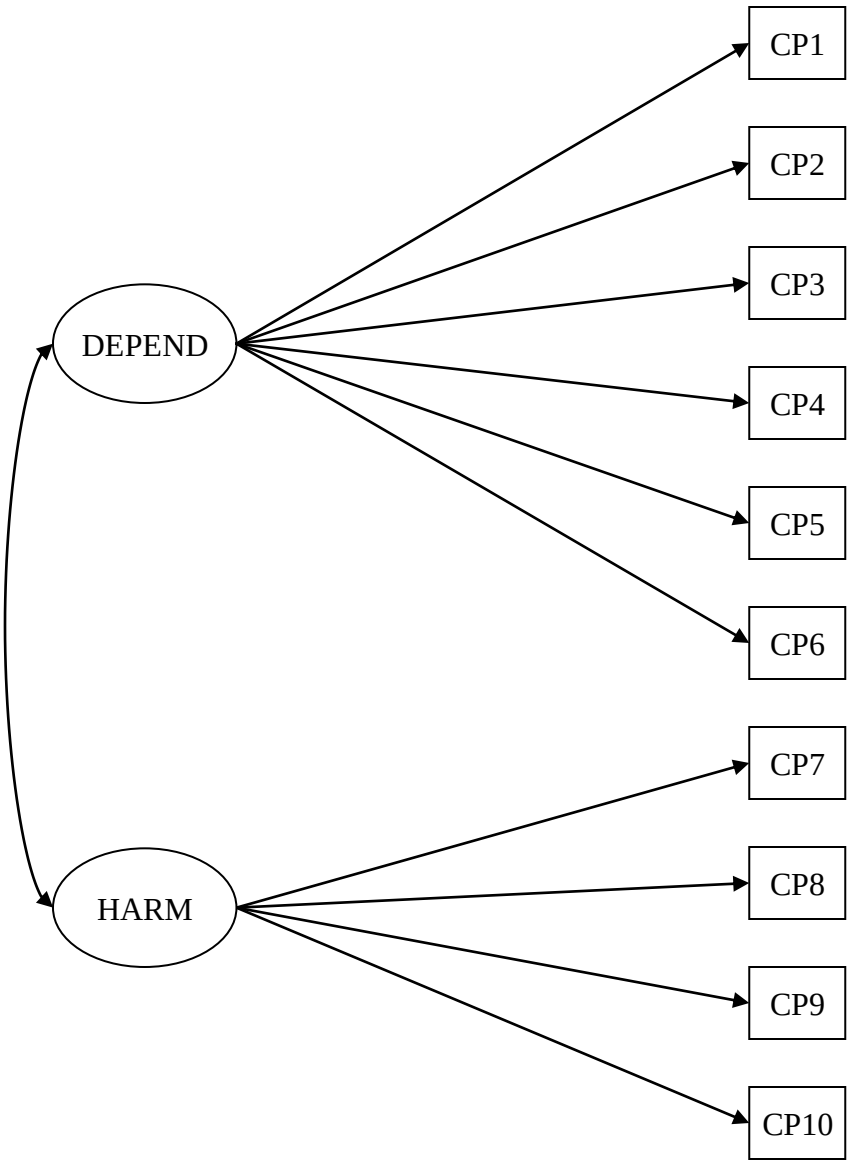



**Figure 3.3.6.** Alternative hypothesized two-factor latent structure of cannabis problems (CP), with one factor of dependence (DEPEND) and a second factor of harmful socially maladaptive or hazardous use (HARM).

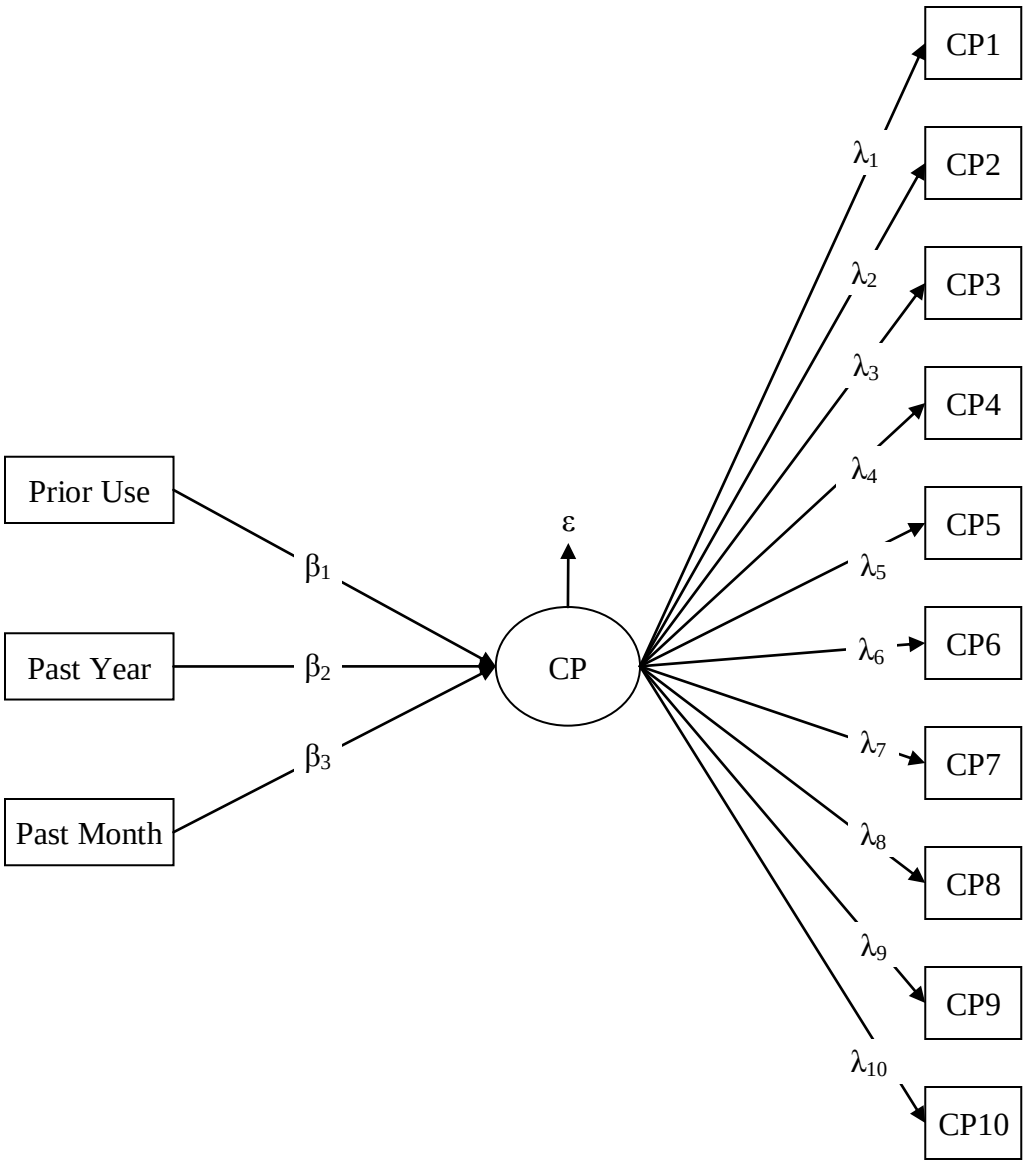



**Figure 3.3.7.** SEM of association between cannabis problems (CP) and blunt smoking recency.

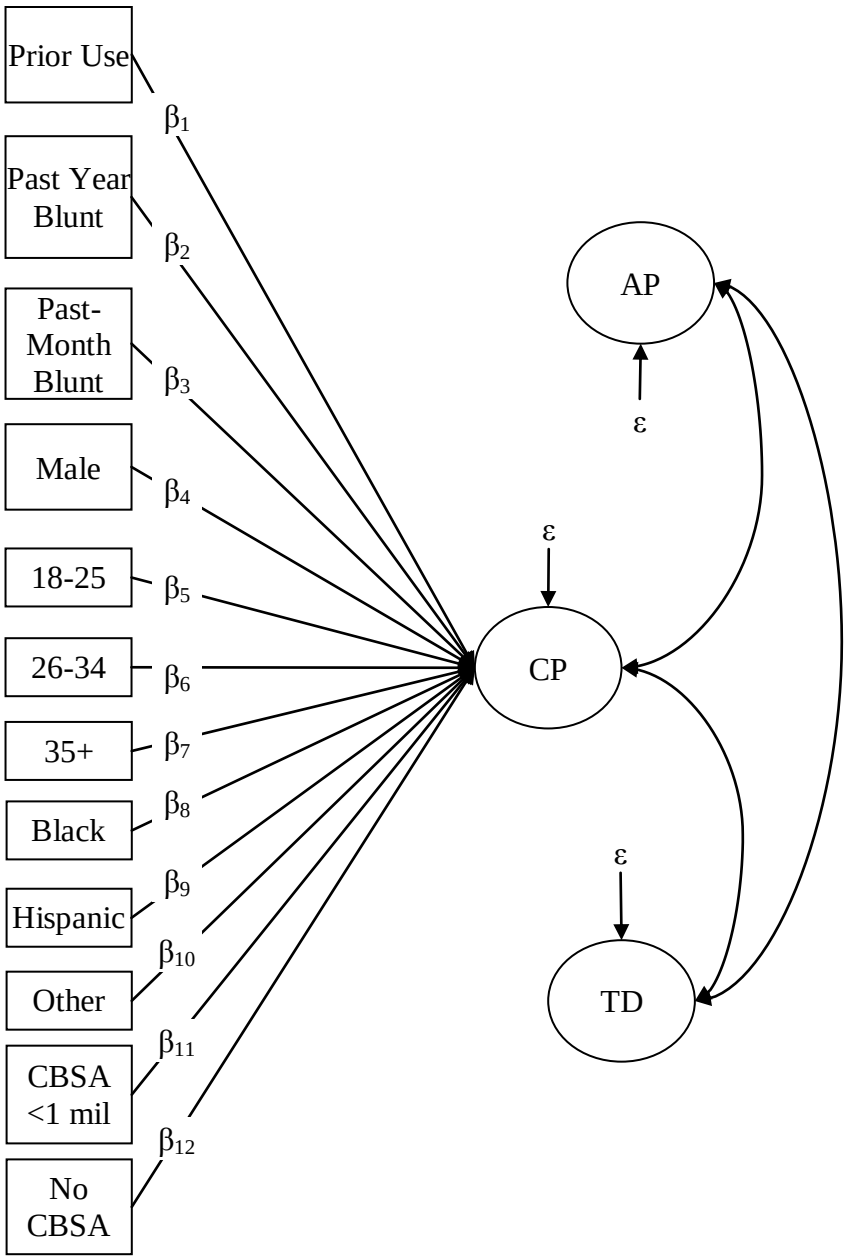



**Figure 3.3.8.** SEM of the association between cannabis problems (CP) and blunt smoking recency with statistical control for background characteristics and factor correlation with alcohol problems (AP) and tobacco dependence (TD).

3.3.4. Study 4: Time to Cannabis Onset and Cannabis Problems.

**AIM 4.** Estimate the degree to which delaying cannabis onset after the first chance to try drugs might account for later level of cannabis problems among a cross-national sample of adults whose only internationally regulated drug (IRD) use was cannabis.

Study 4 focused on a subsample of respondents whose only internationally regulated drug use (IRD) was cannabis (n=6,609), meaning they had not used cocaine, prescription drugs extra-medically, or drugs defined by the 'other' catch-all category (i.e., heroin, ecstasy, inhalants, etc.). Some WMH sites contributed very few cannabis-only users to the analytical sample (see Table 3.3.1), such Iraq (n=1), China (n=3), and Japan (n=6). Prevalence of cannabis-only use was highest in New Zealand and the United States (29% and 22%, respectively).

**Table 3.3.1.** Frequency and weighted prevalence of cannabis-only use by contributing World Mental Health country.

| Country | Total | No Use/ Other | Cannabis-Only | Prev. % |
|---|---|---|---|---|
| Brazil | 4,994 | 4,745 | 249 | 5.0 |
| Colombia | 4,424 | 4,164 | 260 | 5.9 |
| Mexico | 5,766 | 5,554 | 212 | 3.7 |
| United States | 5,707 | 4,329 | 1,378 | 24.1 |
| Bulgaria | 2,211 | 2,197 | 14 | 0.6 |
| Northern Ireland | 1,980 | 1,770 | 210 | 10.6 |
| Romania | 2,357 | 2,341 | 16 | 0.7 |
| Iraq | 4,288 | 4,287 | 1 | <0.1 |
| Israel | 4,816 | 4,367 | 449 | 9.3 |
| Lebanon | 1,032 | 992 | 40 | 3.9 |
| Nigeria | 2,132 | 2,098 | 34 | 1.6 |
| Japan | 1,293 | 1,287 | 6 | 0.5 |
| China | 1,618 | 1,615 | 3 | 0.2 |
| New Zealand | 12,988 | 9,251 | 3,737 | 28.8 |
| **Total**[a] | 55,606 | 48,997 | 6,609 | 11.9 |

[a]Respondents with missing or bad data on cannabis smoking were excluded (n=68).

Initial analyses explored the distribution of cannabis dependence (CD) by WMH country, cigarette smoking status, alcohol dependence, lifetime MDE, and background characteristics (i.e., sex, age, income, education, employment, marital status, and parent's highest level of education) using contingency tables. Weighted prevalence of CD was estimated across categories of these relevant covariates. Histogram plots were used to explore the distribution of discrete continuous variables, such as age of first IRD opportunity, age of cannabis onset, and time to cannabis onset (TCO). Mean values on these items were compared across CD case status. Time to cannabis onset logically should have a lower bound of zero, which would indicate opportunity and use occurred at the same age. However, there were instances of negative values on TCO, and these respondents were exclude from analyses (n=185; representing 2.8% of the sample).

The next step involved series of logistic regression models, in which the task was to estimate the association between CD and TCO. Since CD was coded as a binary outcome, a generalized linear model with a logit link function was used to estimate the change in the log odds of becoming a case of CD for each unit increase in TCO. The following equation depicts the logistic regression formula:

$$\log\frac{(p)}{(1-p)} = \beta_0 + \sum \beta_i x_i$$

Where $p$ is the probability of the outcome occurring, $\beta_0$ is the baseline log odds of the outcome occurring, and $\beta_i$ is the log odds of outcome occurrence for every unit change in $x_i$ as compared to $x_i = 0$. The initial logistic regression model included as covariates only TCO and age of first IRD opportunity. Subsequent models first included statistical control for WMH country, sex, and

age, and then for additional background characteristics, cigarette smoking status, and lifetime MDE.

In the post-estimation exploratory analyses, a single latent trait measurement of cannabis problems (CP) was modeled using features of cannabis dependence and maladaptive cannabis use items (Figure 3.3.9). A series of SEMs regressed the factor scores of CP on TCO, age of first IRD, age, sex, indicator for WMH site, current cigarette smoking status, a latent trait of alcohol problems (AP), income, education, marital status, and parent's highest level of education. All analyses accounted for sample probability weights and the complex survey design. Logistic regression analyses were done using Stata 12 (StataCorp, 2011). Factor analyses and SEMs were conducted in Mplus version 7 (Muthén & Muthén, 2012).

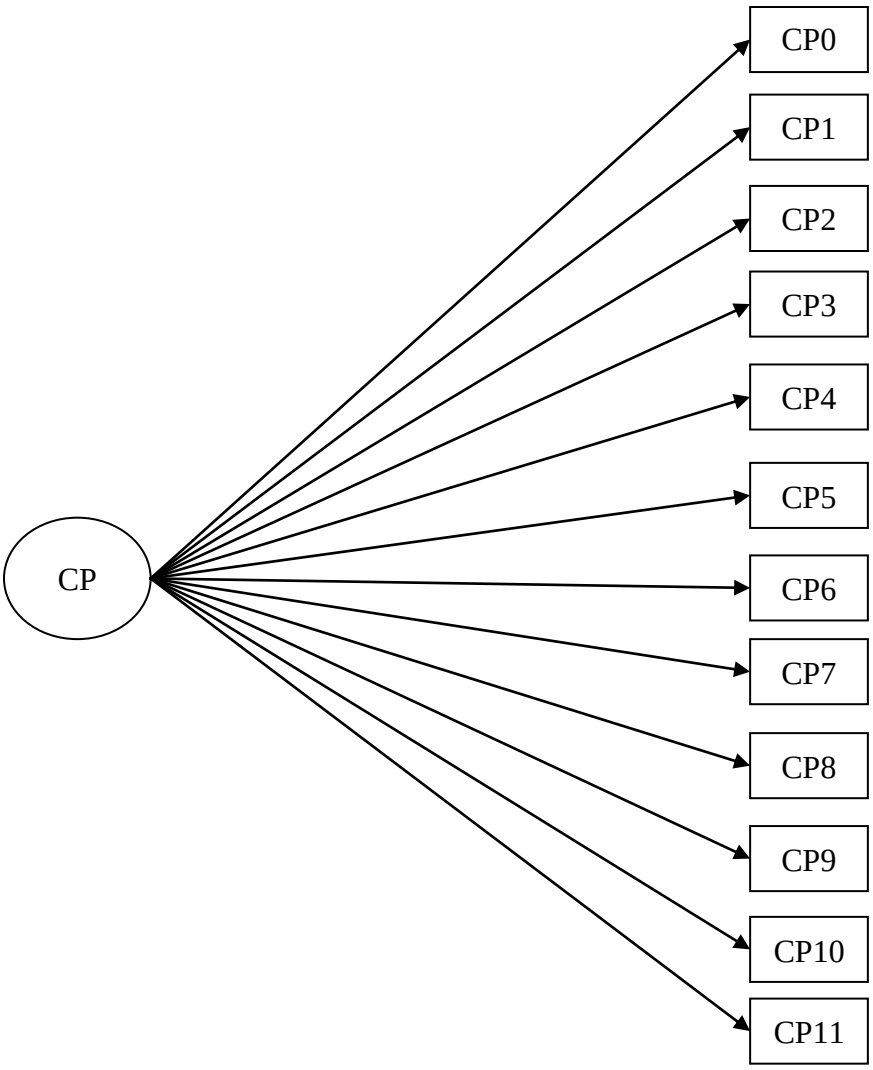



**Figure 3.3.9.** Latent measurement model of cannabis problems (CP) in WMH.

# CHAPTER 4. RESULTS

The initial sections of the results chapter (4.1 and 4.2) build upon the earliest dissertation project work concerning the link between cannabis smoking and depression spells (as discussed in Chapter 2). Afterwards, I initiated a dissertation study intended to replicate and expand upon these findings; for this study, I turned to pertinent data from the U.S. National Surveys on Drug Use and Health (NSDUH). The fruits of that research I judge to be a reflection of an example of investigator-initiated research, completed during the course of my doctoral studies, involving no more than minimal guidance from my primary dissertation committee advisor, J.C. Anthony (JCA), whose involvement primarily was advisor-appropriate polishing of concepts, approach, and manuscript copy-editing. This research was subsequently published in a peer-reviewed journal (see Fairman & Anthony, 2012), but was 'in press' at the time the committee members approved the proposal for this dissertation. With encouragement from JCA, these results have been included here in section 4.1 of the dissertation. It is my judgment that this prior research should be woven into the fabric of my dissertation research. Nonetheless, it has not been counted toward the 'three paper threshold' customarily set for dissertation research programs in our department. Instead, it qualifies as a fourth separate study as part of the overall dissertation program of research. This study certainly contributed toward my development as an independent investigator in epidemiology. Nevertheless, the dissertation committee was asked to judge the merits of the dissertation's evidence and significance irrespective of this initial Fairman-Anthony contribution, based on the remaining three results sections (4.2-4.4).

### 4.1. Study 1: Early-Onset Cannabis Smoking and Depression Spells.

Table 4.1.1 describes the study sample in terms of selected background characteristics cross-classified by depression spell case and non-case status. About 1 in 10 adults in the sample had experienced a depression spell at age 18 or in subsequent adult years. Cases were more likely to be female, white, and older than 25 years of age, have a post-high school education, and divorced or separated.

From Table 4.1.2, the proportion of cases who had smoked cannabis before age 18 (14%) was identical to those who had started later (14%). Depression spells were over-represented among cannabis users with the longest elapsed time of cannabis involvement (11 years or longer, 19%). Varying proportions of depression spells occurred among early-onset users of tobacco cigarettes (12%) and early onset users of alcohol (12%).

Results from the logistic regression analysis prior to covariate adjustment showed a two-fold excess odds of a later depression spell for early-onset cannabis smokers as compared to never cannabis smokers (estimated odds ratio, OR = 2.2; Table 4.1.2, Unadjusted Model) . While the estimate for adult-onset cannabis smokers was nearly the same (OR = 2.0), a statistical test of differences revealed these two estimates to be distinct (p=0.029; not shown in table). When the estimates were adjusted for elapsed time of cannabis involvement, tobacco onset, alcohol onset, sex, age, race/ethnicity, and survey year, there was a attenuation towards null (Early-onset: OR = 1.7; Adult-onset: OR = 1.8), but both estimates remained statistically significant at $p<0.001$. In contrast to the estimates from models without covariate adjustments, there was no statistically significant difference between the odds ratio estimates for early-onset and adult-onset cannabis users (p=0.286; data not shown in table).

**Table 4.1.1.** Sample Characteristics of Depression Spell Cases (n=173,775)

| Characteristic | Depression spell ≥ 18 years | | Never experienced a depression spell | |
|---|---|---|---|---|
| | n | % (wt) | n | % (wt) |
| Total | 16,108 | 10% | 157,667 | 90% |
| Age Group | | | | |
| 18-25 | 5,654 | 7% | 77,988 | 93% |
| 26-34 | 2,892 | 11% | 23,133 | 89% |
| 35-49 | 4,978 | 12% | 32,806 | 88% |
| 50 or older | 2,584 | 10% | 23,740 | 90% |
| Sex | | | | |
| Male | 5,536 | 8% | 77,190 | 92% |
| Female | 10,572 | 13% | 80,477 | 87% |
| Race/Ethnicity | | | | |
| White | 11,302 | 12% | 100,370 | 88% |
| Black | 1,643 | 8% | 19,841 | 92% |
| Hispanic | 1,995 | 8% | 24,731 | 92% |
| Asian | 390 | 5% | 6,035 | 95% |
| Other[a] | 778 | 11% | 6,690 | 89% |
| Highest Level of Education | | | | |
| Less than High School | 2,038 | 8% | 28,465 | 92% |
| High School Graduate | 4,736 | 9% | 52,954 | 91% |
| Some College | 5,315 | 12% | 44,281 | 88% |
| College Graduate | 4,019 | 12% | 31,967 | 88% |
| Employment Status | | | | |
| Full-time | 8,505 | 10% | 83,690 | 90% |
| Part-time | 2,773 | 11% | 28,867 | 89% |
| Unemployed | 1,042 | 12% | 10,267 | 88% |
| Other[b] | 3,788 | 10% | 34,843 | 90% |
| Marital Status | | | | |
| Married | 6,252 | 9% | 60,275 | 91% |
| Widowed | 499 | 10% | 3,937 | 90% |
| Divorced/Separated | 2,783 | 17% | 12,863 | 83% |
| Never married | 6,574 | 9% | 80,592 | 91% |

Data: US National Surveys on Drug Use and Health, 2005-2009
Weighted proportion (wt)
[a] Included Native Americans, Alaskan Natives, Native Hawaiians, Other Pacific Islanders, and more than one race/ethnicity.
[b] Included, but not in the labor force.

**Table 4.1.2.** Prevalence of Depression Spell Cases and Association with Cannabis, Cigarette, and Alcohol Onset, and Years of Cannabis Involvement.

| | | Depression Spell Cases | | Unadjusted Models[a] | | | Adjusted Model[b] | | |
|---|---|---|---|---|---|---|---|---|---|
| **Drug Exposure** | **Total** | **n** | **Prev. %** | **OR** | **(95% CI)** | **P-value** | **OR** | **(95% CI)** | **P-value** |
| Cannabis Onset | | | | | | | | | |
| Never Used | 90,298 | 6,185 | 7 | 1.0 | | | 1.0 | | |
| Early-Onset | 54,891 | 6,454 | 14 | 2.2 | (2.0,2.3) | <0.001 | 1.7 | (1.5,1.9) | <0.001 |
| Adult-Onset | 28,089 | 3,439 | 14 | 2.0 | (1.9,2.1) | <0.001 | 1.8 | (1.6,1.9) | <0.001 |
| Missing | 497 | 30 | 7 | 1.0 | (0.7,1.5) | 0.986 | 1.1 | (0.7,1.7) | 0.745 |
| Years of Cannabis Involvement | | | | | | | | | |
| Never Used | 90,298 | 6,185 | 7 | 1.0 | | | 1.0 | | |
| < 1 year | 14,688 | 1,502 | 12 | 1.7 | (1.6,1.9) | <0.001 | 0.8 | (0.7,0.9) | 0.002 |
| 1-10 years | 35,963 | 4,217 | 13 | 2.0 | (1.9,2.1) | <0.001 | 1.0 | (0.9,1.1) | 0.498 |
| 11 or more | 11,317 | 2,153 | 19 | 2.9 | (2.7,3.2) | <0.001 | 1.4 | (1.2,1.6) | <0.001 |
| Missing | 21,509 | 2,051 | 12 | 1.7 | (1.6,1.9) | <0.001 | NA | | |
| Cigarette Onset | | | | | | | | | |
| Never Used | 54,945 | 3,510 | 7 | 1.0 | | | 1.0 | | |
| Early-Onset | 88,770 | 9,697 | 12 | 1.9 | (1.8,2.1) | <0.001 | 1.2 | (1.1,1.3) | <0.001 |
| Adult-Onset | 29,190 | 2,848 | 10 | 1.5 | (1.3,1.6) | <0.001 | 1.1 | (1.0,1.2) | 0.104 |
| Missing | 870 | 53 | 6 | 0.9 | (0.6,1.4) | 0.689 | 1.0 | (0.6,1.5) | 0.942 |
| Alcohol Onset | | | | | | | | | |
| Never | 22,123 | 945 | 5 | 1.0 | | | 1.0 | | |
| Early-Onset | 96,531 | 10,300 | 12 | 2.9 | (2.6,3.3) | <0.001 | 2.0 | (1.7,2.3) | <0.001 |
| Adult-Onset | 53,733 | 4,790 | 9 | 2.1 | (1.8,2.3) | <0.001 | 1.7 | (1.5,1.9) | <0.001 |
| Missing | 1,388 | 73 | 6 | 1.2 | (0.9,1.8) | 0.226 | 1.1 | (0.7,1.5) | 0.737 |

Prevalence (Prev), Odds ratio (OR), Confidence interval (CI)

[a] Univariable logistic regressions between depression spells and each drug exposure.

[b] Multivariable logistic regression model included all variables in the table plus sex, age, race, and survey year.

From Table 4.1.2, one can also see estimates for the unadjusted and covariate-adjusted depression spell-related odds relative to tobacco cigarette and alcohol onset, and it should be noted that EOCU is the acronym that refers to early-onset cannabis use, as defined above. Adult-onset tobacco cigarette smoking was not associated with depression spells after adjustment for covariates in the model (unadjusted OR = 1.5; $p<0.001$; adjusted OR = 1.1; $p=0.104$). Nevertheless, there was a very small excess odds that linked adult-onset occurrence of a depression spell with early-onset tobacco smoking (adjusted OR = 1.2; $p<0.001$), independent of the EOCU-depression association. Both early- and adult-onset alcohol drinking were noteworthy covariates in the covariate-adjusted model (OR = 2.0 and 1.7, respectively; both $p<0.001$). Post-estimation analysis revealed that the difference between these two odds ratio estimates was statistically significant at $p<0.001$ (data not shown in table).

Readers might speculate about the degree to which these findings might be affected had statistical models with covariate adjustment for additional influences, such as education, income, employment, use of other internationally regulated drugs, etc. (Hereinafter, early-onset cannabis use sometimes is abbreviated with the acronym, EOCU.)

Given the nature of the data, these covariates might very well be consequences of either cannabis smoking or depression, and it was decided to evaluate their potential influence on the EOCU-depression relationship in post-estimation exploratory analyses. Using an add-one-in (AOI) approach, where only one additional covariate is added to the statistical model at a time, most of these covariates induced little variation in the EOCU estimate (Figure 4.1.1). Only use of other internationally regulated drugs besides cannabis shifted the EOCU estimate towards null to a noteworthy degree, but even then the estimate remained above null (OR=1.2; 95% CI = 1.1, 1.3).

An alternative approach estimated a statistical model in which all relevant covariates were evaluated together in the same model in order to evaluate their potential combined effects on the EOCU estimate (Figure 4.1.1). A backwards elimination model building procedure was considered to avoid over adjustment and produce a parsimonious model. However, no single covariate met the *a priori* p-value threshold of $p>0.20$. In this combined model, the EOCU-estimate was statistically null (OR=1.0; 95% CI = 0.9, 1.1).

In order to evaluate which covariates might have an overdue influence on the main study estimate, a leave-one-out (LOO) procedure was used (Figure 4.1.1). This iterative procedure eliminated one model covariate at a time. A non-null estimate for the EOCU-depression spells relationship was observed only when excluding years of cannabis involvement (OR=1.2; 95% CI= 1.1,1 .3) or other illegal drug use (OR=1.3; 95% CI= 1.2, 1.5). Spearman rank order correlations showed a strong correlation between the cannabis onset variable and years of cannabis involvement ($\rho=0.87$), and a weak correlation between cannabis onset and other internationally regulated drug use ($\rho=0.44$; a table of the Spearman correlation matrix can be found in the Appendix).

In the second set of exploratory analyses (Table 4.1.3), onset of cannabis smoking before age 15 or at 18 years or older was found to be associated with occurrence of later adult-onset depression spells, even with covariate adjustment, in a comparison with never users of cannabis as a reference or comparison subgroup (OR = 1.9; OR = 1.7, respectively; Table 4.1.3). In these analyses there was a probe for possibly evidence that a different age threshold for EOCU might have produced stronger associations between EOCU and occurrence of the depression spell. No evidence was found to require reporting of quantitative estimates from this set of exploratory

analyses (contrast between ≤15 years and 18 years or older p-value = 0.190; data not shown in a table).

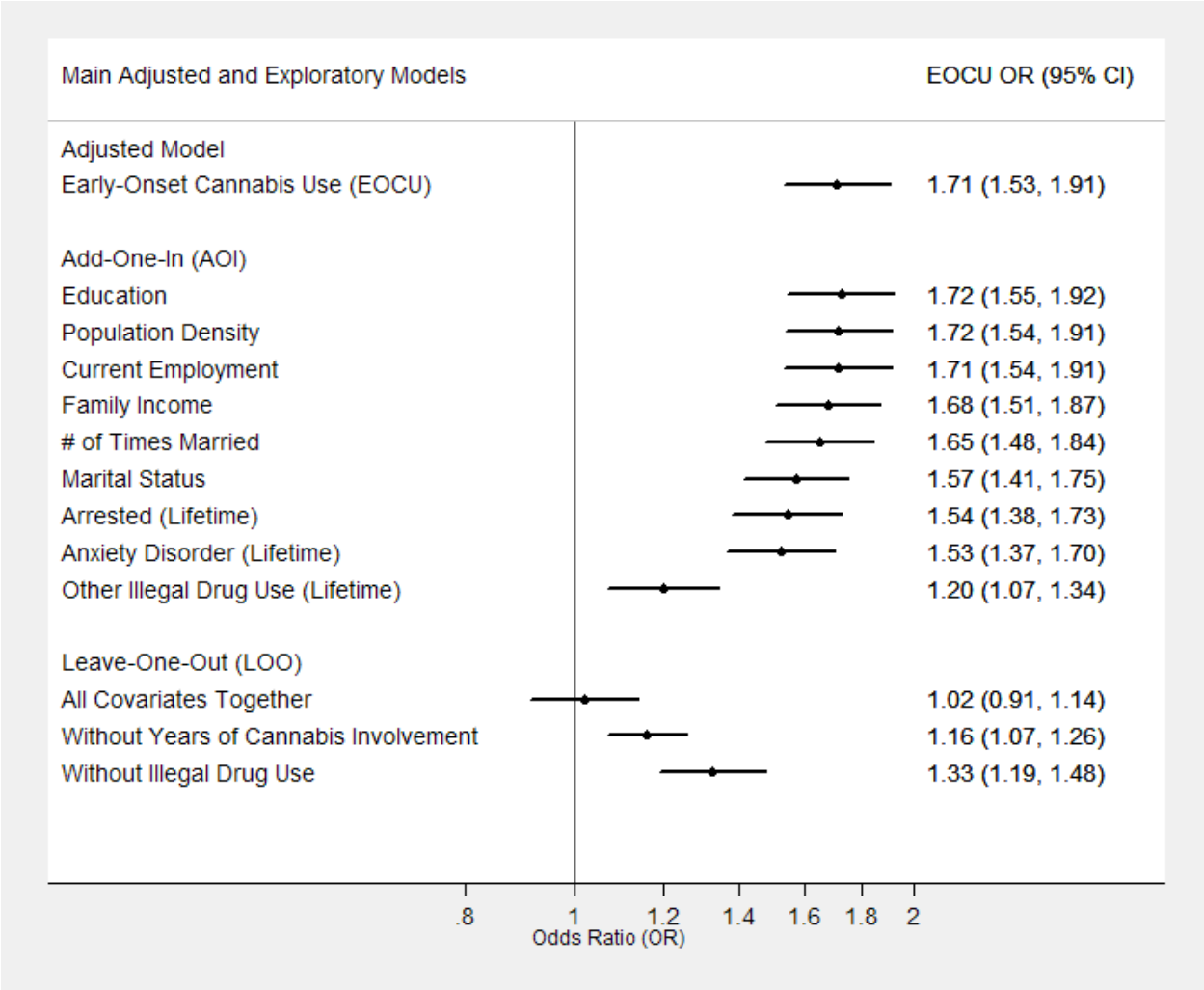



**Figure 4.1.1.** Post-estimation exploratory analysis of the adjusted early-onset cannabis use (EOCU) estimate with additional statistical control of other covariates using add-one-in (AOI) and leave-one-out (LOO) approaches.

**Table 4.1.3.** Exploratory analysis of association between depression spells and fine-grained cannabis onset exposure.

| | Adjusted Model[a] | | |
|---|---|---|---|
| | **OR** | **(95% CI)** | **P-value** |
| Cannabis Onset | | | |
| Never Used | 1.0 | | |
| ≤ 15 years | 1.9 | (1.6, 2.1) | <0.001 |
| 15 years | 1.7 | (1.5, 2.0) | <0.001 |
| 16 years | 1.6 | (1.4, 1.8) | <0.001 |
| 17 years | 1.6 | (1.4, 1.9) | <0.001 |
| ≥ 18 years | 1.7 | (1.6, 1.9) | <0.001 |

[a]Model adjusted for elapsed time of cannabis involvement, tobacco cigarette onset, alcohol onset, sex, age, race/ethnicity, and survey year.

## 4.2. Study 2: Cannabis Problems and Functional Impairment Attributed to Recently Active Depression Spells.

### 4.2.1. Sample Characteristics by Depression Status

An estimated 14% of the total NSDUH sample surveyed from 2009-2011 had a major depressive episode (MDE) at some point in their lives (Table 4.2.1). Among these lifetime cases, a little more than half were a recently active depression spell cases in the past year (53%; n=13,743). Differences in background characteristics were apparent by recently active depression spell status. For example, the population sample tended to more evenly female vs. male (52% vs. 48%), however, past-year depression spell cases were much more likely to be female (65% vs. 35%).

**Table 4.2.1.** Characteristics of U.S. National Surveys on Drug Use and Health from 2009 to 2011 by Depression Status (n=172,042).

| | | Total | | Never MDE/ Unknown | | Prior Depression[a] | | Recently Active Depression Spell[b] | |
|---|---|---|---|---|---|---|---|---|---|
| | | (n=172,042) | | (n=148,291) | | (n=10,008) | | (n=13,743) | |
| Variable | Categories | n | (%) | n | (%) | n | (%) | n | (%) |
| Sex | Male | 82,896 | (48.5) | 75,222 | (50.4) | 3,423 | (37.3) | 4,251 | (34.8) |
| | Female | 89,146 | (51.5) | 73,069 | (49.6) | 6,585 | (62.7) | 9,492 | (65.2) |
| Age | 12-17 | 55,583 | (9.7) | 48,376 | (9.7) | 2,642 | (7.4) | 4,565 | (11.3) |
| | 18-25 | 57,503 | (13.4) | 49,314 | (13.2) | 3,351 | (12.4) | 4,838 | (16.0) |
| | 26-34 | 17,160 | (14.3) | 14,509 | (14.0) | 1,279 | (17.0) | 1,372 | (15.9) |
| | ≥35 | 41,796 | (62.6) | 36,092 | (63.1) | 2,736 | (63.2) | 2,968 | (56.9) |
| Race/ Ethnicity | White | 106,701 | (66.7) | 90,756 | (65.5) | 6,875 | (77.6) | 9,070 | (72.4) |
| | Black | 22,024 | (11.9) | 19,712 | (12.3) | 872 | (7.1) | 1,440 | (10.0) |
| | Hispanic | 27,958 | (14.7) | 24,595 | (15.2) | 1,364 | (10.0) | 1,999 | (12.2) |
| | Other | 15,359 | (6.7) | 13,228 | (6.9) | 897 | (5.3) | 1,234 | (5.4) |
| Income | <$20K | 39,845 | (18.4) | 33,804 | (17.9) | 2,277 | (17.0) | 3,764 | (25.6) |
| | $20K-$49,999 | 57,739 | (32.8) | 49,660 | (32.9) | 3,323 | (30.4) | 4,756 | (33.4) |
| | $50K-$74,999 | 28,486 | (17.1) | 24,631 | (17.2) | 1,741 | (17.1) | 2,114 | (16.2) |
| | ≥$75K | 45,972 | (31.7) | 40,196 | (32.0) | 2,667 | (35.5) | 3,109 | (24.9) |
| County Metro | Large Metro | 74,812 | (53.2) | 64,899 | (53.5) | 4,229 | (51.8) | 5,684 | (51.0) |
| | Small Metro | 60,965 | (30.7) | 52,192 | (30.5) | 3,664 | (32.6) | 5,109 | (32.2) |
| | Non-Metro | 36,265 | (16.0) | 31,200 | (16.0) | 2,115 | (15.6) | 2,950 | (16.8) |

[a] Prior depression was defined as individuals with a lifetime occurrence of major depressive episode (MDE), but not have a depression spell within the past 12 months.
[b] Recently active depression spell was defined as a two-week or more spell of depressed mood or anhedonia with allied symptoms.

4.2.2. Descriptive Statistics and Distribution of Impairment Outcome Indicators

On average, recently active depression spell cases experienced a moderate amount of functional impairment (Table 4.2.2). In a quarter of the cases, impairment was severe or very severe. Small differences were observed in the mean values for individual SDS items. Depression spell cases experienced more impairment in social life (mean, M=6.2; 95%CI=6.1, 6.3) and relationships/family life (M=5.8; 95%CI=5.7, 5.9), than for work/school (M=5.0;

95%CI=4.9, 5.1) or home management/chores domains (M=5.6; 95%CI=5.5, 5.7). Half were unable to carry out daily activities due to a depression spell for at least 5 or more days out of the past year, while a quarter were impaired for a month or longer. Less than 1% of recently active depression spell cases had missing data any of the first four SDS items, while about 4% were missing on 'Days unable to carry out activities' in the past year (SDS5). The distribution of each SDS item, along with an overlay of a normal density curve with the mean and standard deviation of the SDS item is displayed below (Figures 4.2.1-4.2.4). The distribution of impairments with work/school and home management/chores had the least amount of skew, while impairments in social life and close relationships were slightly negatively skewed.

**Table 4.2.2.** Descriptive Statistics of Sheehan Disability Scale (SDS) Items Among Sample of Past-Year Depression Spell Cases (n=13,743)

| Variable | Description | n | Min | Max | Q50 | Q75 | Mean | Std. Err. | 95% CI | |
|---|---|---|---|---|---|---|---|---|---|---|
| SDS1 | Home Management/Chores | 13663 | 0 | 10 | 5 | 7 | 5.6 | 0.04 | 5.5 | 5.7 |
| SDS2 | Work/School | 13648 | 0 | 10 | 5 | 7 | 5.0 | 0.05 | 4.9 | 5.1 |
| SDS3 | Relationships/Family Life | 13688 | 0 | 10 | 6 | 8 | 5.8 | 0.05 | 5.7 | 5.9 |
| SDS4 | Social Life | 13690 | 0 | 10 | 6 | 8 | 6.2 | 0.05 | 6.1 | 6.3 |
| SDS5 | Days unable to carry out activities | 13155 | 0 | 365 | 5 | 30 | 60.7 | 2.01 | 56.7 | 64.7 |

Data: US National Surveys on Drug Use and Health, 2009-2011

Q = Quartile; Std. Err. = Standard Error; CI = Confidence Interval

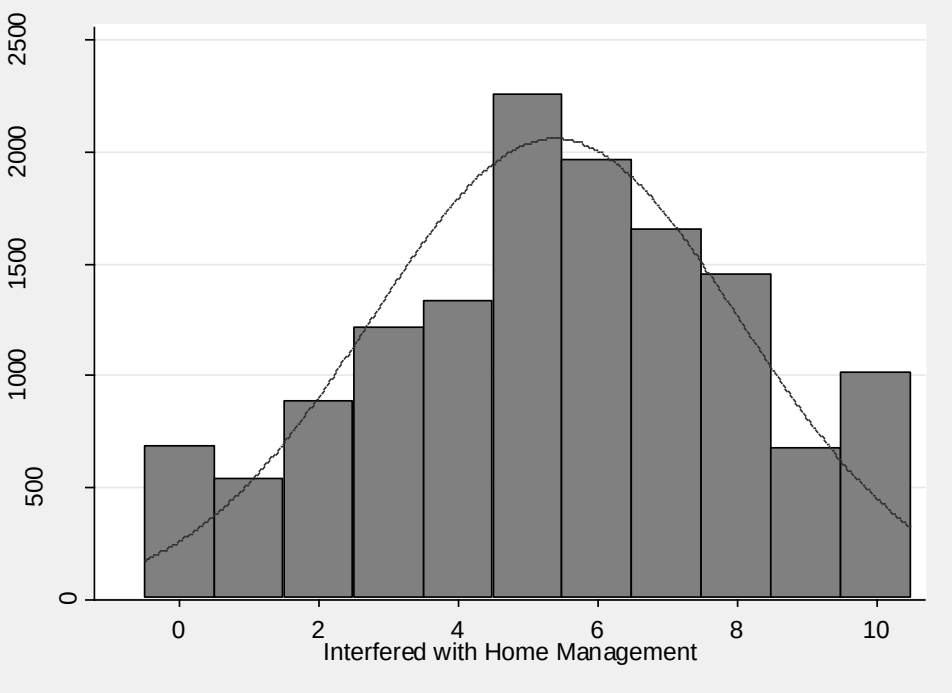



**Figure 4.2.1.** Distribution of home management/chore impairment among recently active depression spell cases.

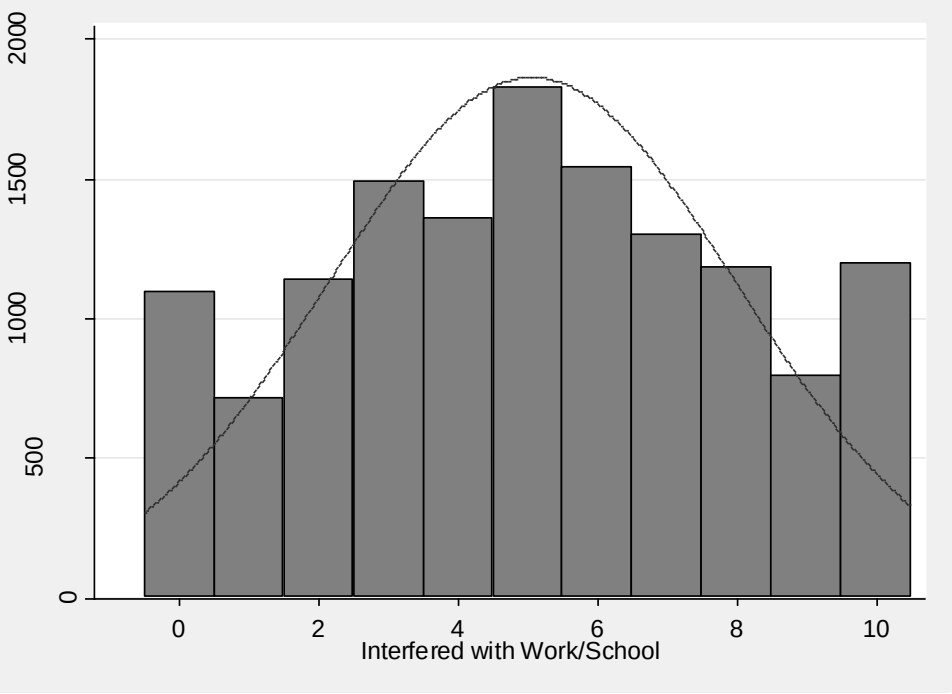



**Figure 4.2.2.** Distribution of work/school impairment among recently active depression spell cases.

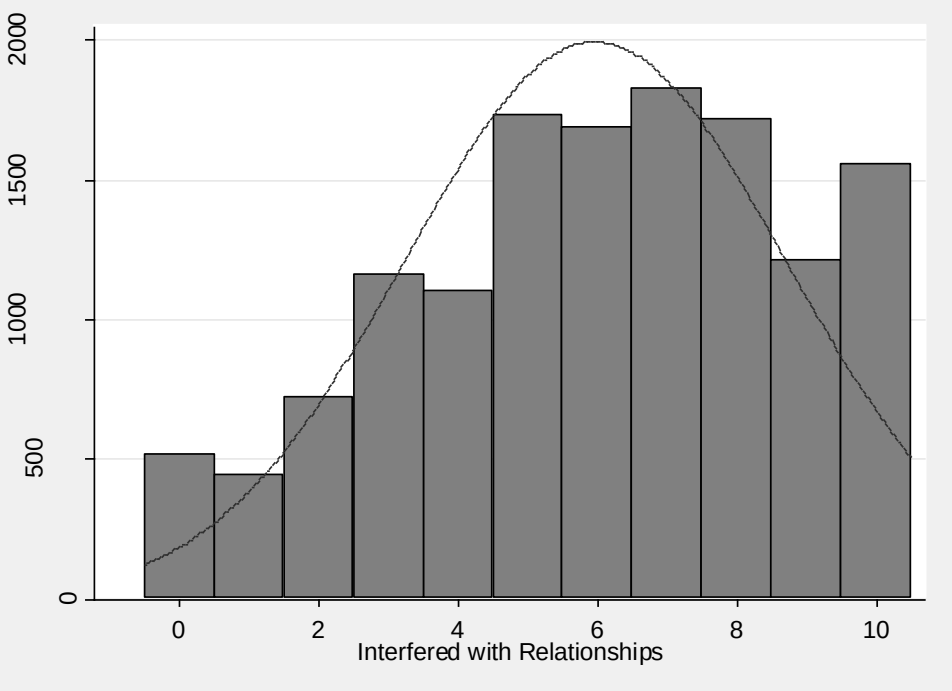



**Figure 4.2.3.** Distribution of close relationship impairment among recently active depression spell cases.

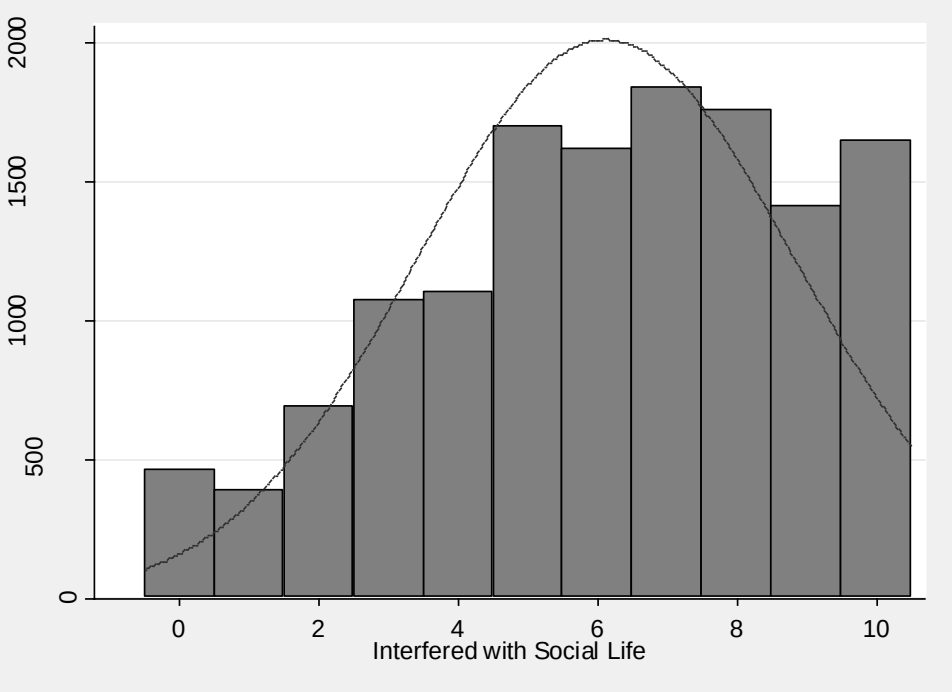



**Figure 4.2.4.** Distribution of social life impairment among recently active depression spell cases.

4.2.3. Factor Analysis

There were moderately strong to very strong positive inter-correlations among SDS items (Table 4.2.3). For example, the item on impairments with social life and the item on relationships/family had the strongest correlation (0.72). 'Days unable to carry out activities' tended to be less correlated with other items, except for impairment with work/school (0.58). Factor analysis was conducted using all five SDS items in a hypothesized single factor model (see Figure 3.3.1 from Chapter 3). This model of overall functional impairment provided a generally unsatisfactory fit to the data (CFI = 0.926; TFI = 0.770; RMSEA = 0.112). Examination of modification indices indicated that allowing covariance between the residuals for impairment items 'relationships/family' and 'social life' would improve model fit (Figure 4.2.5). Freeing this parameter resulted in a substantial improvement (drop) in the chi-square value ($\Delta \chi^2$=494.1; df=1). It also made substantive sense for there to be residual correlation between interpersonal items of functional impairment that might not be captured by the IMPAIR latent trait. Re-specification of the measurement model improved the fit (CFI=0.97; TLI=0.92; RMSEA=0.04). In exploratory analyses, this model re-specification did not alter the final estimates. Model fit to individual, single factor latent models of cannabis problems (CP; Figure 4.2.6), alcohol problems (AP; Figure 4.2.7), and tobacco dependence (TD; Figure 4.2.8) all were an excellent fit to the data (CFI>0.990; TLI>0.990; RMSEA<0.05 for each model).

**Table 4.2.3.** Correlation Between Sheehan Disability Scale (SDS) Items of Functional Impairment Due to Depression Spells (n=13,081).

| Observed Variable | | SDS1 | SDS2 | SDS3 | SDS4 | SDS5 |
|---|---|---|---|---|---|---|
| SDS1 | Home Management/Chores | 1.00 | | | | |
| SDS2 | Work/School | 0.60 | 1.00 | | | |
| SDS3 | Relationships/Family Life | 0.52 | 0.53 | 1.00 | | |
| SDS4 | Social Life | 0.53 | 0.51 | 0.72 | 1.00 | |
| SDS5 | Days unable to carry out activities | 0.49 | 0.58 | 0.41 | 0.44 | 1.00 |

Data: US National Surveys on Drug Use and Health, 2009-2011

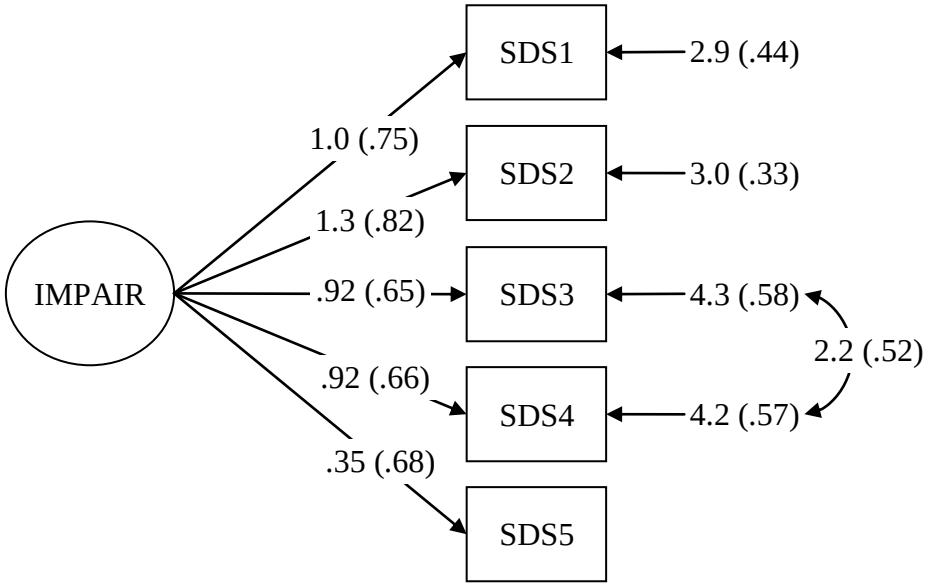



**Figure 4.2.5.** Post-hoc re-specification of the measurement model of functional impairment attributed to depression (IMPAIR). Standardized coefficients in parentheses. CFI=0.97; TLI=0.92; RMSEA=0.04

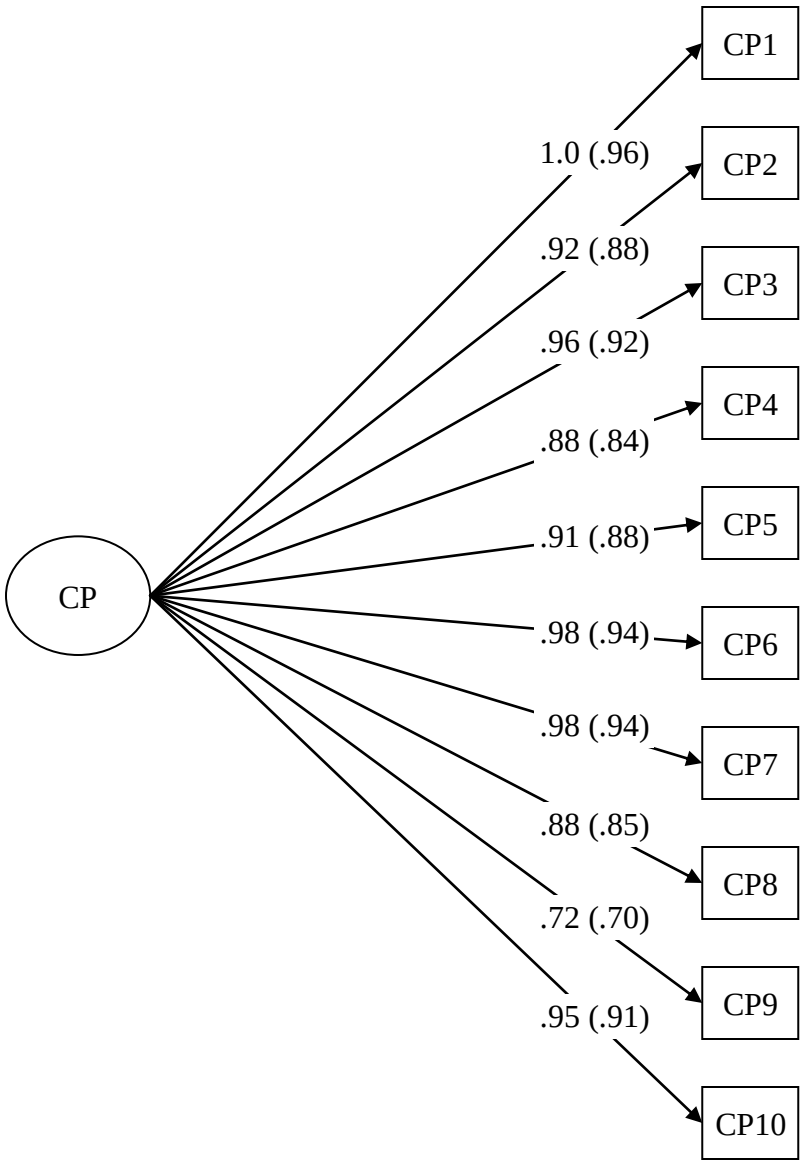



**Figure 4.2.6.** Measurement model of cannabis problems (CP). Standardized estimates in parentheses. CFI=0.995; TLI=0.994; RMSEA=0.02.

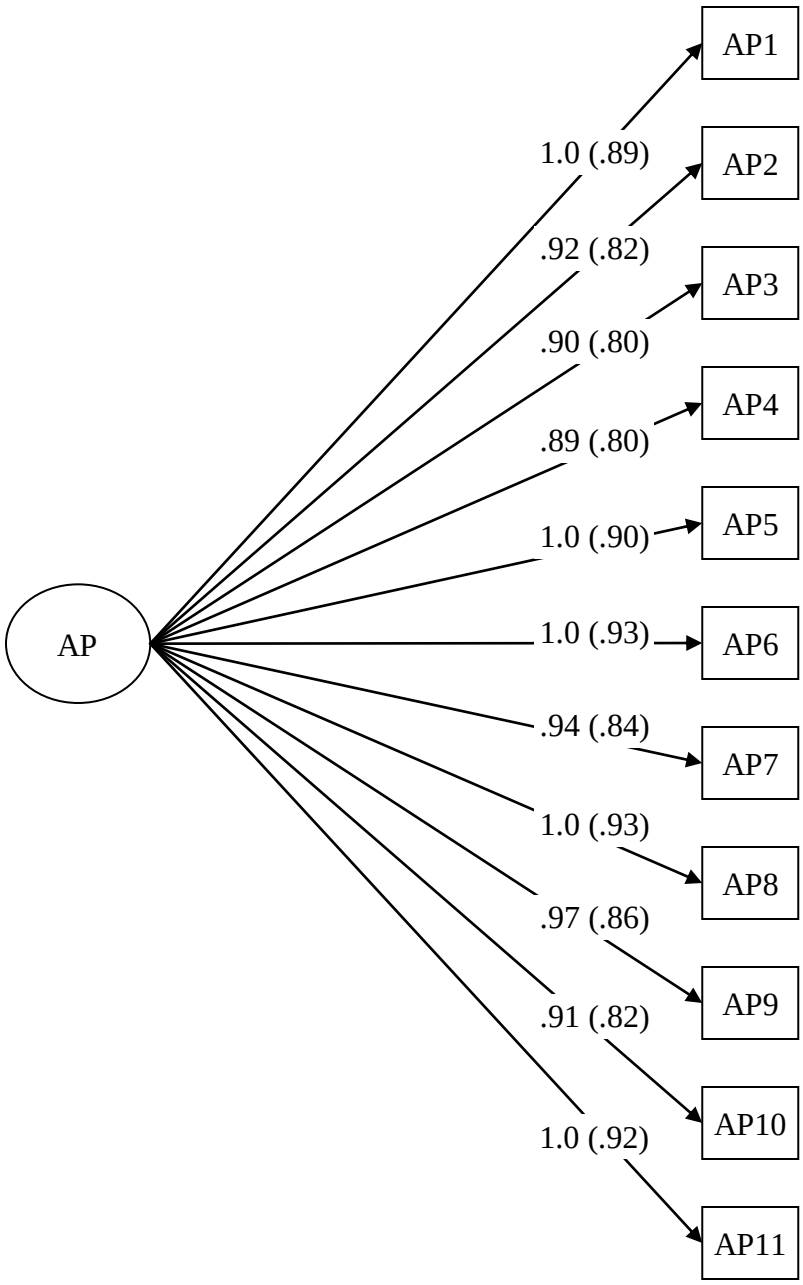



**Figure 4.2.7.** Measurement model of alcohol problems (AP). Standardized estimates in parentheses. CFI=0.992; TLI=0.991; RMSEA=0.02.

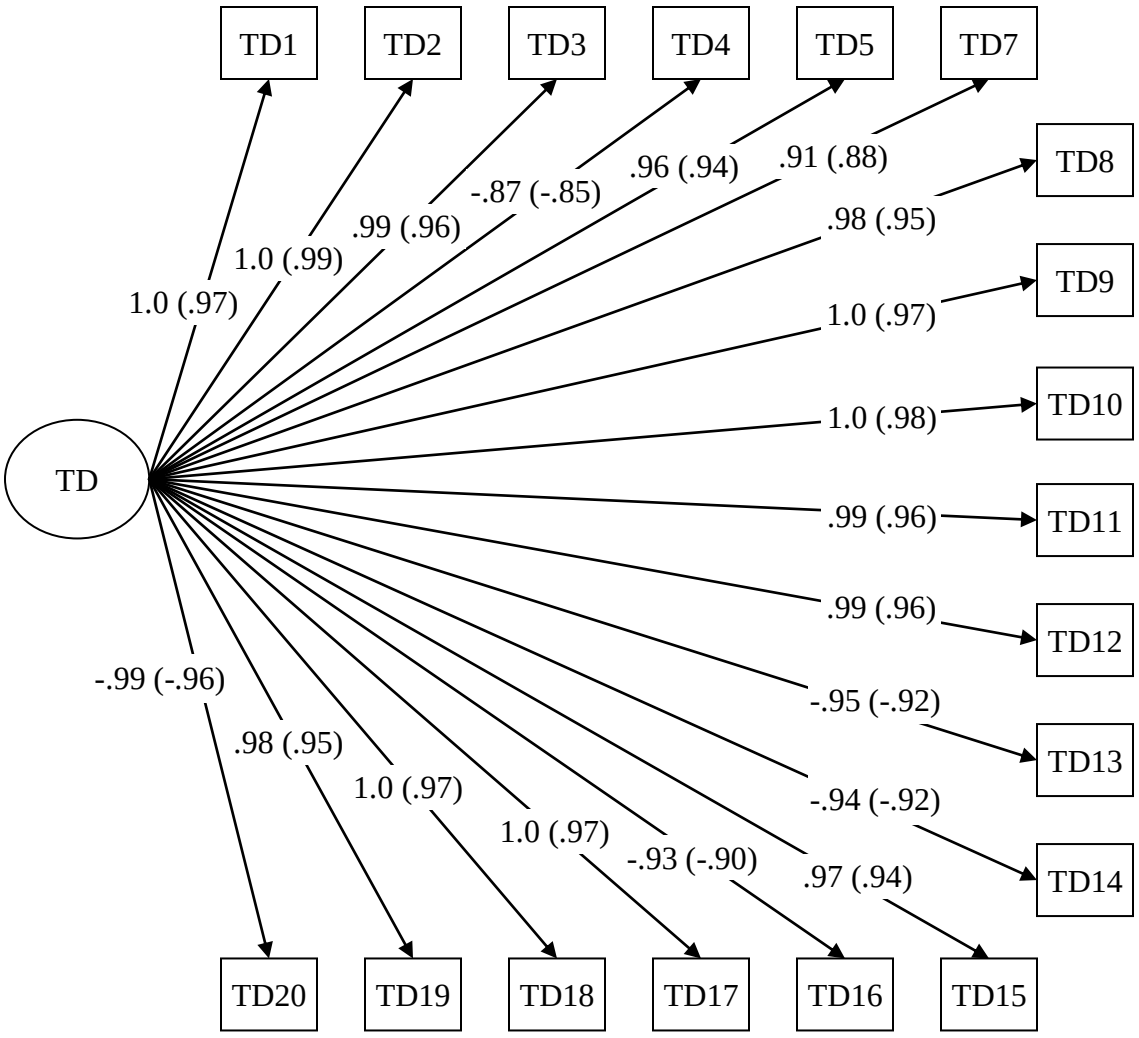



**Figure 4.2.8.** Measurement model of tobacco dependence. Standardized estimates in parentheses. CFI=0.996; TLI=0.996; RMSEA=0.05.

4.2.4. Modeling Relationship Between Cannabis Problems and Functional Impairment Attributed to Depression Spells

As estimated under a model that expresses functional impairment attributed to depression spells (FIDS) as a function of level of cannabis problems (CPL) and other covariates, functional impairment attributed to depression spells was at higher levels when level of cannabis problems was at higher levels. Level of CP was positively associated with higher levels of impairment attributed to depression in the unadjusted and adjusted models (Figure 4.2.9, Figure 4.2.10, and

Figure 4.2.11). Models adjusting for the level of alcohol problems, tobacco dependence, and background factors such as sex, age, and race/ethnicity partially, but did not completely, attenuate the hypothesized association linking CP on IMPAIR construct (unadjusted $\beta$=0.32 vs. adjusted $\beta$=0.20). Final models (e.g., Fig 4.2.11) also showed increased functional impairment attributed to depression for those with higher levels of tobacco dependence ($\beta$=0.39; $p<0.001$).

In a comparison of standardized estimates, the hypothesized effect of TD on IMPAIR was estimated as being greater than for CP (B=0.23 vs. 0.11; data not shown in figure). These estimates were statistically distinct, as determined by comparing the final model to one in which the CP and TD paths to IMPAIR were assumed to be equivalent, which proved to provide a less satisfactory model fit. By contrast, the level of alcohol problems appeared to have no relationship with functional impairment attributed to depression.

Other model estimates were of note, but are presented here solely as a source of leads in future research, whereas the estimates of primary importance in this research involve cannabis effect estimation. Blacks had higher levels of impairment compared to Whites, while being 18-25 year old was associated with lower impairment levels compared to 12-17 year olds. Females had lower levels of all three latent dimensions of drug problems. For cannabis problems, there was a positive association for 18-25 year olds, which was inverse for older age groups. This was contrasted for levels of AP and TD, which were higher for all age groups older than 12-17. As compared to Whites, Blacks experienced lower levels of AP and TD, while Hispanics and "Other" racial/ethnic groups had lower levels of TD only.

4.2.5. Post-Estimation Exploratory Analyses

Additional post-estimation exploratory analyses to test model assumptions not depicted in tables or figures are described here, with additional coverage in the Discussion chapter notes on study limitations. First, it was previously mentioned that the hypothesized measurement model of functional impairment attributed to depression was re-specified by allowing the residuals for SDS3 and SDS4 items to correlate, which improved the fit of the model. Re-analysis of the final model without this modification revealed no appreciable differences in the estimates reported. Second, the conceptual model assumed CP level determined the level of impairment, however, since the measurement of both constructs pertained to the same 12 month period prior to interview, this assumption may not be tenable. Indirect supporting evidence came from an exclusion of those whose first depression spell occurred prior to or at the same age as their cannabis onset (n=3,803), which would violate the temporality assumption of the model. Though based on a smaller sample size (n=9,529), the estimated effect of CP level on impairment was nearly the same ($\beta$=0.19; p=0.035).

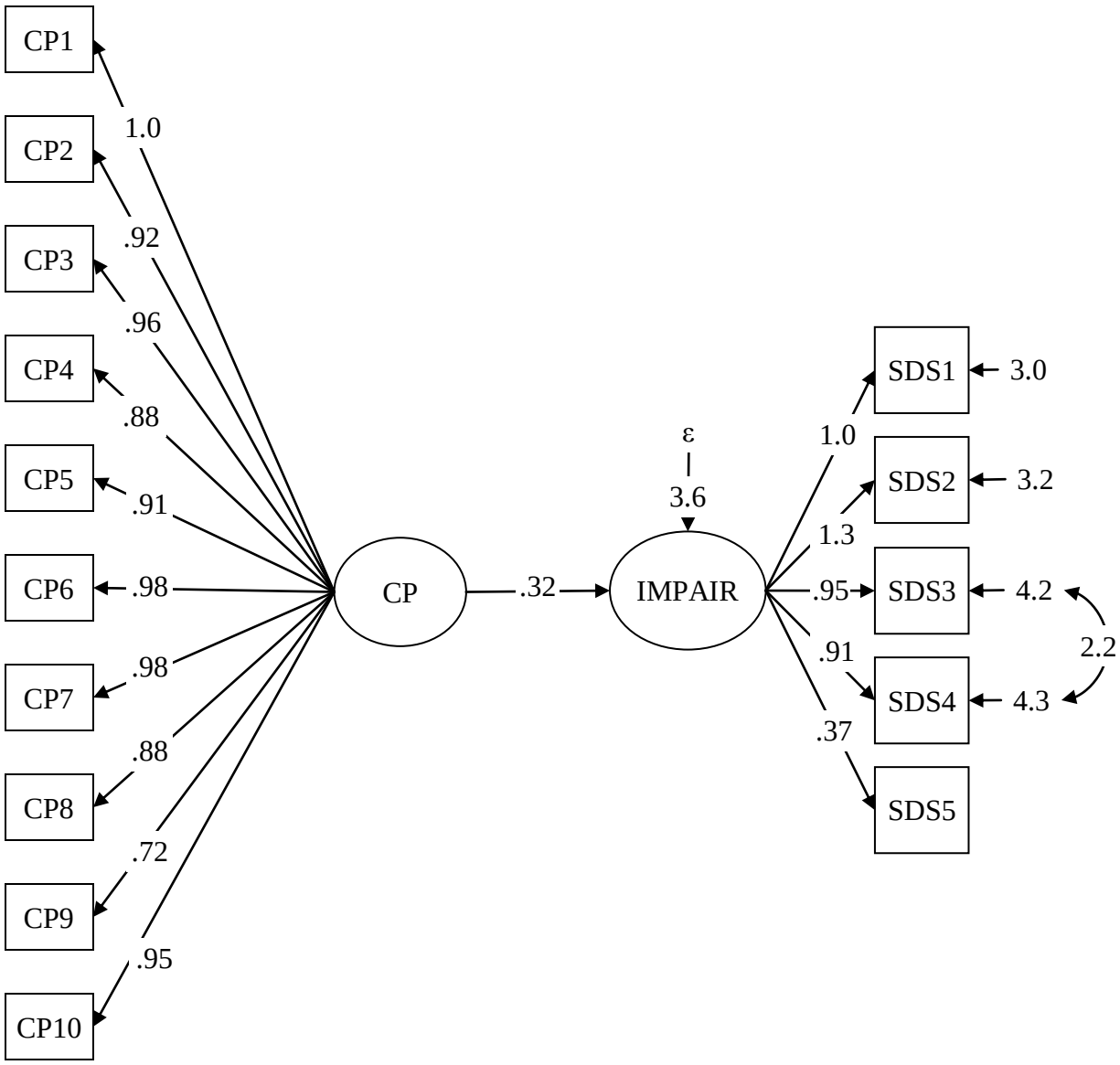



**Figure 4.2.9.** Association between functional impairment attributed to depression (IMPAIR) and cannabis problems (CP). CFI=0.992; TLI=0.99; RMSEA=0.01.

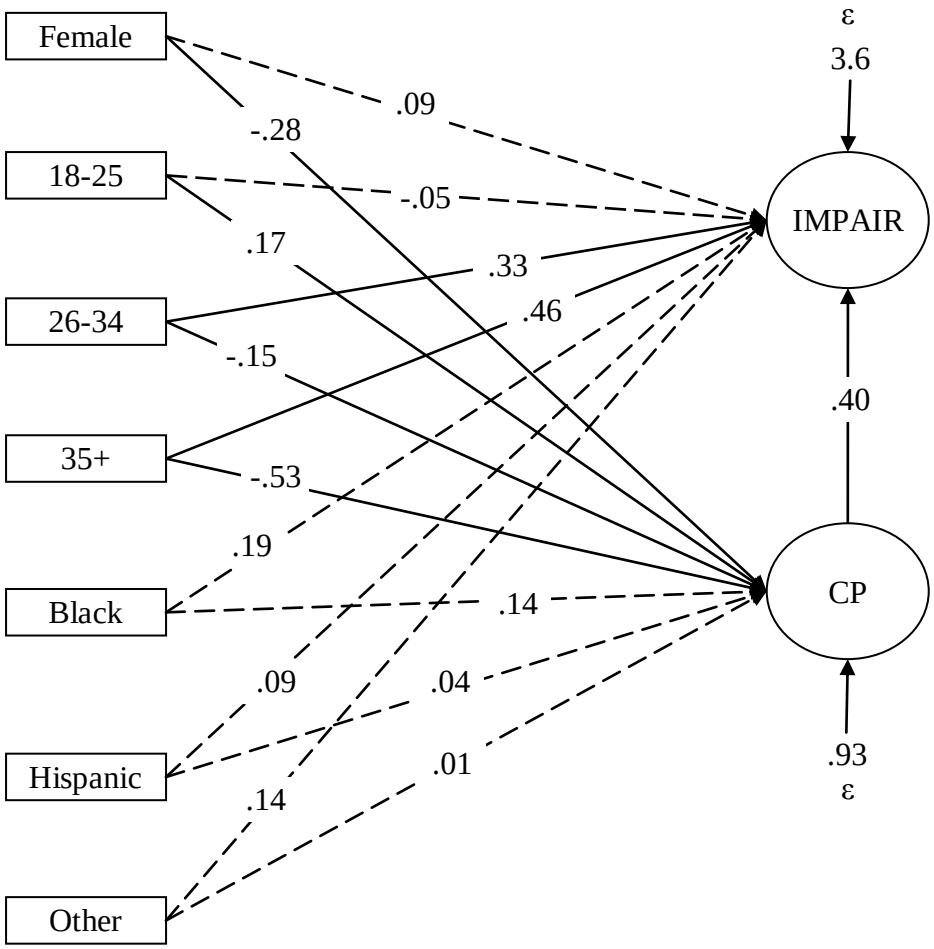



**Figure 4.2.10.** Association between functional impairment attributed to depression (IMPAIR), cannabis problems (CP), and background characteristics. Reference groups were males, 12-17 year olds, and non-Hispanic Whites. Dashed arrows indicate estimates with p>0.05. CFI=0.97; TLI=0.96; RMSEA=0.02.

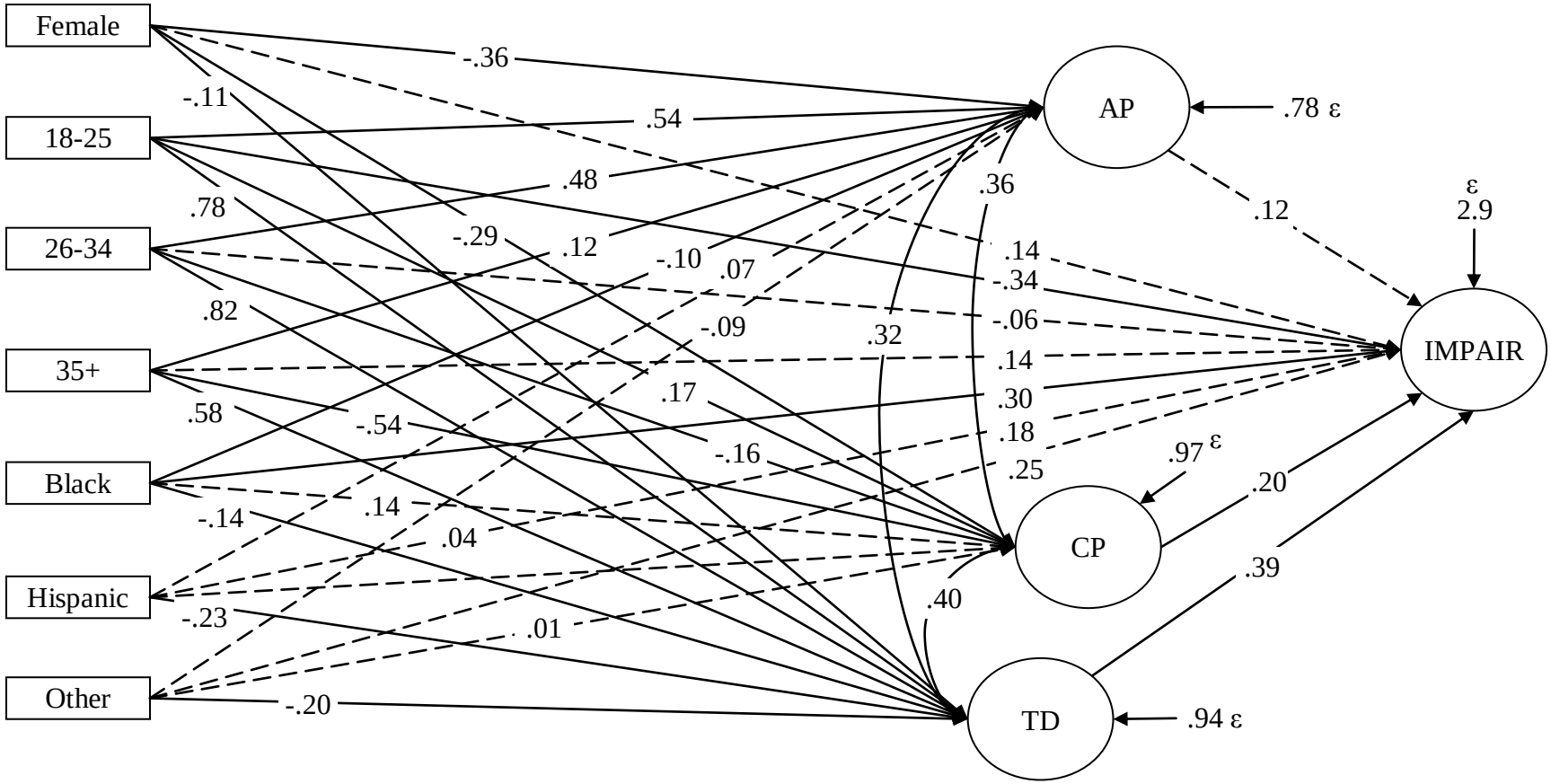



**Figure 4.2.11.** Association between functional impairment attributed to depression (IMPAIR), cannabis problems (CP), alcohol problems (AP), tobacco dependence (TD), and background characteristics. Dashed arrows indicate estimates with p>0.05. CFI=0.998; TLI=0.998; RMSEA=0.01.

## 4.3. Study 3: Cannabis Problems and History of Blunt Smoking.

Here, study aims focus on possible blunt effects that increase levels of cannabis problems.

### 4.3.1. Characteristics of Past-Year Cannabis Users

Distribution of background characteristics of past-year cannabis users (n=77,047) differed from the total population sampled by the NSDUH from 2004-2011 (Table 4.3.1). For example, the weighted proportions of males to females in the total sample were roughly equal, but past-year cannabis users tended to be male (61%). Youths 18-25 years olds made up over a third of past-year cannabis users (36%), despite being an estimated 13% of the population. Differences by race/ethnicity and population density were comparatively small.

### 4.3.2. Prevalence of Blunt Smoking and Cannabis Problems

An estimated 70% of past-year cannabis users smoked a blunt at least once in their lifetimes (Table 4.3.2). Slightly under one-half (47%) smoked a blunt in the past year, while about a quarter smoked one as recently within the past month. Estimates were fairly stable from 2004 to 2011, but there was a statistically significant increase in blunt use during this period. For example, estimated cumulative incidence increased from 66% to 72% during this period.

Overall, past-year cannabis users commonly experienced ‘spending a great deal of time getting or using cannabis’ (42%) and tolerance (29%), while few experienced ‘trouble with the law’ (3%) (Table 4.3.3). Blunt smokers had about twice the prevalence of each cannabis problem as compared to their non-blunt smoking peers. For example, 13% of past-year cannabis users who never smoked a blunt had experienced tolerance as compared to 33% of those who had

smoked a blunt. A similar pattern emerged when comparing past-year cannabis users who smoked a blunt in the past year versus those who had not.

**Table 4.3.1.** Characteristics of Total Sample Surveyed and Past-Year Cannabis User Analytical Sample

| | Total | | Past-Year Cannabis Use | | | |
|---|---|---|---|---|---|---|
| | | | No | | Yes | |
| | (n=450,002) | | (n=372,955) | | (n=77,047) | |
| | n | (wt%) | n | (wt%) | n | (wt%) |
| **Sex** | | | | | | |
| Female | 233,672 | (51.5) | 199,680 | (52.9) | 33,992 | (39.4) |
| Male | 216,330 | (48.5) | 173,275 | (47.1) | 43,055 | (60.6) |
| **Age** | | | | | | |
| 12-17 Years Old | 146,438 | (10.1) | 126,265 | (9.8) | 20,173 | (12.3) |
| 18-25 Years Old | 149,844 | (13.3) | 107,229 | (10.6) | 42,615 | (35.9) |
| 26-34 Years Old | 45,269 | (14.3) | 38,308 | (13.6) | 6,961 | (20.3) |
| 35 or Older | 108,451 | (62.3) | 101,153 | (66.0) | 7,298 | (31.5) |
| **Race or Ethnicity** | | | | | | |
| White | 284,551 | (67.9) | 233,958 | (67.7) | 50,593 | (69.6) |
| Black/African-American | 57,056 | (11.8) | 47,061 | (11.6) | 9,995 | (13.8) |
| Native Am/Alaskan Native | 6,723 | (0.5) | 4,938 | (0.5) | 1,785 | (0.7) |
| Native HI/Other Pacific Islander | 2,044 | (0.3) | 1,680 | (0.3) | 364 | (0.3) |
| Asian | 15,435 | (4.4) | 14,153 | (4.7) | 1,282 | (1.8) |
| More than one race | 13,733 | (1.2) | 10,612 | (1.1) | 3,121 | (1.9) |
| Hispanic | 70,460 | (14.0) | 60,553 | (14.2) | 9,907 | (11.9) |
| **Population Density** | | | | | | |
| CBSA ≥ 1 million | 184,252 | (51.2) | 151,947 | (50.8) | 32,305 | (54.1) |
| CBSA < 1 million | 216,376 | (40.4) | 178,822 | (40.5) | 37,554 | (39.6) |
| Not in CBSA | 49,374 | (8.4) | 42,186 | (8.6) | 7,188 | (6.3) |

Data: US National Surveys on Drug Use and Health, 2004-2011.

Weighted percentage (wt%); Core based statistical area (CBSA)

**Table 4.3.2.** Prevalence of Blunt Smoking History Among Past-Year Cannabis Users by Individual Survey Years.

| | Total | | Ever Smoked Blunts | | | Smoked Blunts in Past Year | | | Smoked Blunts in Past Month | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Year | n | % | Prev. | 95% CI | | Prev. | 95% CI | | Prev. | 95% CI | |
| 2004 | 9,528 | 12.4 | 65.9 | (64.1, | 67.8) | 44.5 | (42.9, | 46.1) | 21.8 | (20.6, | 23.0) |
| 2005 | 9,348 | 12.1 | 66.4 | (64.4, | 68.4) | 44.2 | (42.6, | 45.7) | 23.1 | (21.7, | 24.4) |
| 2006 | 8,971 | 11.6 | 69.8 | (67.2, | 72.4) | 47.5 | (45.4, | 49.7) | 24.6 | (23.0, | 26.1) |
| 2007 | 9,034 | 11.7 | 70.1 | (68.0, | 72.2) | 47.0 | (45.1, | 49.0) | 25.0 | (23.6, | 26.4) |
| 2008 | 9,229 | 12.0 | 71.6 | (69.3, | 74.0) | 48.3 | (46.2, | 50.3) | 25.4 | (24.0, | 26.8) |
| 2009 | 10,022 | 13.0 | 72.2 | (70.0, | 74.3) | 46.5 | (44.5, | 48.6) | 25.3 | (23.8, | 26.9) |
| 2010 | 10,396 | 13.5 | 72.5 | (70.6, | 74.3) | 48.4 | (46.2, | 50.5) | 25.6 | (23.7, | 27.4) |
| 2011 | 10,519 | 13.7 | 72.1 | (70.2, | 74.0) | 47.8 | (45.9, | 49.6) | 26.8 | (25.4, | 28.2) |
| Total | 77,047 | 100.0 | 70.2 | (69.5, | 70.8) | 46.8 | (46.1, | 47.5) | 24.8 | (24.3, | 25.2) |

Data: US National Surveys on Drug Use and Health, 2004-2011

Weighted prevalence (Prev.); Confidence interval (CI)

**Table 4.3.3.** Weighted Prevalence (%) of Cannabis Problems Among Past-Year Cannabis Users.

| | | Total | | Ever Smoked Blunts | | | | Smoked Blunts in Past Year | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | No | | Yes | | No | | Yes | |
| Cannabis Problems (CP) | | % | SE | % | SE | % | SE | % | SE | % | SE |
| CP1 | Spend great deal of time | 41.5 | (0.4) | 18.2 | (0.7) | 48.4 | (0.4) | 23.7 | (0.5) | 55.7 | (0.5) |
| CP2 | Unable to set limits | 7.3 | (0.2) | 3.6 | (0.3) | 8.4 | (0.2) | 4.4 | (0.3) | 9.6 | (0.2) |
| CP3 | Tolerance | 28.5 | (0.3) | 13.2 | (0.5) | 33.0 | (0.4) | 16.3 | (0.4) | 38.2 | (0.4) |
| CP4 | Difficulty cutting down | 6.6 | (0.2) | 4.0 | (0.3) | 7.3 | (0.2) | 4.6 | (0.2) | 8.2 | (0.2) |
| CP5 | Use despite emotional/ physical problems | 8.5 | (0.2) | 5.1 | (0.4) | 9.5 | (0.2) | 5.8 | (0.3) | 10.6 | (0.3) |
| CP6 | Gave up important activities | 11.2 | (0.2) | 6.2 | (0.4) | 12.7 | (0.2) | 7.2 | (0.3) | 14.5 | (0.3) |
| CP7 | Serious role impairment | 7.0 | (0.2) | 3.8 | (0.3) | 7.9 | (0.2) | 4.3 | (0.2) | 9.1 | (0.2) |
| CP8 | Hazardous use | 7.1 | (0.2) | 4.3 | (0.3) | 8.0 | (0.2) | 4.6 | (0.2) | 9.2 | (0.2) |
| CP9 | Trouble with the law | 3.0 | (0.1) | 1.4 | (0.2) | 3.5 | (0.1) | 1.6 | (0.1) | 4.2 | (0.1) |
| CP10 | Problems with family/friends | 5.6 | (0.1) | 3.0 | (0.3) | 6.3 | (0.2) | 3.1 | (0.2) | 7.5 | (0.2) |

Data: US National Surveys on Drug Use and Health, 2004-2011.

4.3.3. Exploratory and Confirmatory Factor Analysis of Cannabis Problems

A correlation matrix of CP items did not reveal a clear pattern of factor structure (Table 4.3.4). An exploratory factor analysis was then conducted using the first half of a random split sample of data from the 2004 NSDUH (n=3,534). Figure 4.3.1 presents a scree plot of eigenvalues (EV). There were two EV larger than one, however, almost 60% of the total variance could be explained by the first factor (EV=5.7), while a second factor would contribute only an additional 13% (EV=1.3). Examining factor loadings from one and two factor solutions revealed additional insights (Table 4.3.5). All items loaded strongly on the single factor, with loadings ranging from 0.56 for 'difficulty cutting down' to 0.85 for 'giving up important activities'. Item loading in the two factor solution did not conform to DSM-IV hypothesized constructs of dependence and abuse. Most items loaded strongly on one factor dominated by socially maladaptive or hazardous problems (CP5-CP10), while a second factor appeared to tap problems related to repetitive use behavior (CP2 and CP4). As noted earlier, 'spend a great deal of time' (CP1) and tolerance (CP3) were common problems, and these items had moderate loadings on both factors.

Confirmatory factor analysis (CFA) was then conducted on the second half of sample data from the 2004 NSDUH (n=3,520). A single latent factor model was compared to a two factor model with CP1-CP6 items loading on a latent trait of dependence (DEPEND), and with CP7-CP10 items loading on a latent trait of socially maladaptive or otherwise harmful cannabis use (HARM). Both models were a good fit to the data (Table 4.3.5: CFI>0.95; TLI>0.95; RMSEA=0.01). However, latent factors were strongly correlated (0.86). Thus, the totality of the evidence favored a single factor, which was used for subsequent analyses.

**Table 4.3.4.** Correlation Matrix of Cannabis Problem (CP) Items Among Past-Year Cannabis Users (n=3,534).

| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| CP1 | Spend great deal of time | 1.00 | | | | | | | | | |
| CP2 | Unable to set limits | 0.56 | 1.00 | | | | | | | | |
| CP3 | Tolerance | 0.67 | 0.47 | 1.00 | | | | | | | |
| CP4 | Difficulty cutting down | 0.50 | 0.71 | 0.39 | 1.00 | | | | | | |
| CP5 | Use despite emotional/ physical problems | 0.56 | 0.48 | 0.57 | 0.46 | 1.00 | | | | | |
| CP6 | Gave up important activities | 0.61 | 0.50 | 0.56 | 0.36 | 0.68 | 1.00 | | | | |
| CP7 | Serious role impairment | 0.47 | 0.44 | 0.50 | 0.34 | 0.66 | 0.79 | 1.00 | | | |
| CP8 | Hazardous use | 0.59 | 0.40 | 0.45 | 0.29 | 0.55 | 0.57 | 0.59 | 1.00 | | |
| CP9 | Trouble with the law | 0.39 | 0.27 | 0.50 | 0.18 | 0.47 | 0.48 | 0.68 | 0.52 | 1.00 | |
| CP10 | Problems with family/friends | 0.57 | 0.41 | 0.52 | 0.33 | 0.66 | 0.72 | 0.73 | 0.68 | 0.63 | 1.00 |

Data: Random half-split sample of data from US National Survey on Drug Use and Health, 2004

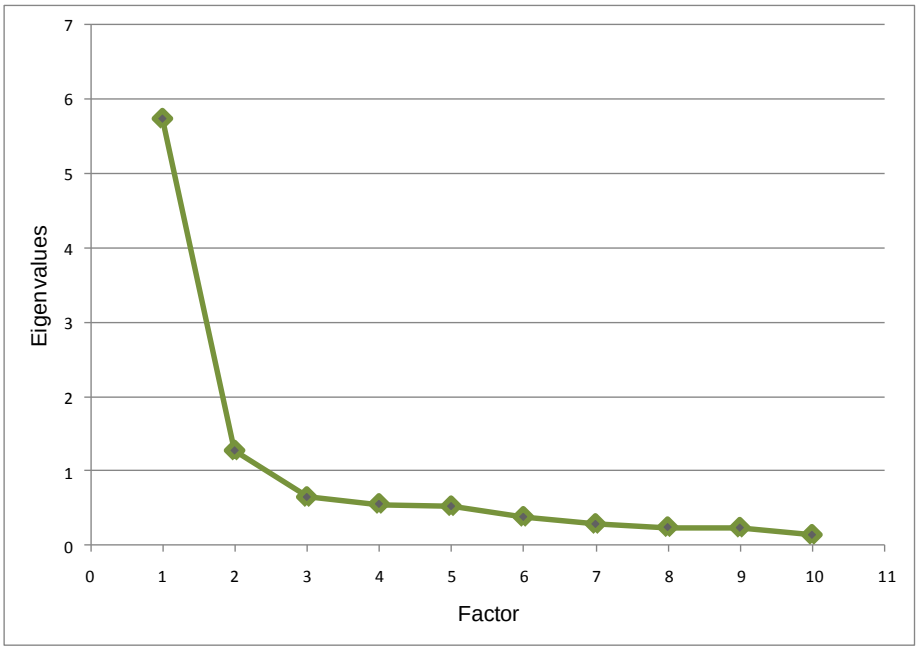



**Figure 4.3.1.** Scree Plot of Eigenvalues from Exploratory Factor Analysis of Cannabis Problems. Random Half-Split Sample of Data from 2004 National Surveys on Drug Use and Health (n=3,534).

**Table 4.3.5.** Exploratory and Confirmatory Factor Analysis of Cannabis Problems, Standardized and Unstandardized Factor Loadings Using Random Split Sample of Data from 2004 US National Surveys on Drug Use and Health.

| Cannabis Problems | | | Exploratory (n =3,534) | | | Confirmatory (n =3,520) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 1 Factor | 2 Factors | | 1 Factor | | | | 2 Factor | | | |
| | | % | 1 | 1 | 2 | Latent | β | B | SE | Latent | β | B | SE |
| CP1 | Spend great deal of time | 42 | 0.79 | 0.36 | 0.57 | CP | 0.70 | 1.00 | | DEPEND | 0.73 | 1.00 | |
| CP2 | Unable to set limits | 8 | 0.65 | 0.05 | 0.78 | CP | 0.59 | 0.84 | 0.06 | DEPEND | 0.60 | 0.83 | 0.06 |
| CP3 | Tolerance | 28 | 0.71 | 0.38 | 0.46 | CP | 0.68 | 0.96 | 0.06 | DEPEND | 0.69 | 0.95 | 0.06 |
| CP4 | Difficulty cutting down | 8 | 0.56 | 0.10 | 0.84 | CP | 0.59 | 0.84 | 0.06 | DEPEND | 0.60 | 0.83 | 0.06 |
| CP5 | Use despite emotional/ physical problems | 10 | 0.78 | 0.61 | 0.26 | CP | 0.72 | 1.02 | 0.07 | DEPEND | 0.74 | 1.02 | 0.07 |
| CP6 | Gave up important activities | 12 | 0.85 | 0.78 | 0.12 | CP | 0.86 | 1.22 | 0.07 | DEPEND | 0.89 | 1.23 | 0.07 |
| CP7 | Serious role impairment | 8 | 0.84 | 0.94 | 0.09 | CP | 0.86 | 1.22 | 0.06 | HARM | 0.92 | 1.00 | |
| CP8 | Hazardous use | 9 | 0.71 | 0.63 | 0.15 | CP | 0.59 | 0.85 | 0.07 | HARM | 0.63 | 0.68 | 0.04 |
| CP9 | Trouble with the law | 4 | 0.65 | 0.78 | 0.13 | CP | 0.71 | 1.01 | 0.08 | HARM | 0.75 | 0.81 | 0.04 |
| CP10 | Problems with family/friends | 7 | 0.82 | 0.84 | 0.02 | CP | 0.75 | 1.06 | 0.07 | HARM | 0.78 | 0.85 | 0.04 |
| Model Fit Indices | | | | | | | | | | | | | |
| | CFI | | 0.96 | | 0.99 | | 0.95 | | | | 0.96 | | |
| | TLI | | 0.96 | | 0.99 | | 0.95 | | | | 0.96 | | |
| | RMSEA | | 0.01 | | 0.05 | | 0.01 | | | | 0.01 | | |
| | Factor Correlation | | NA | | 0.55 | | NA | | | | 0.86 | | |

Data: US National Survey on Drug Use and Health, 2004

SE, standard error; β, standardized estimates; B, unstandardized estimates; CFI, comparative fit index; TFI, Tucker-Lewis index; RMSEA, root mean square error of approximation

4.3.4. Recent Blunt Smoking and Level of Cannabis Problems

Factor scores for the latent trait of cannabis problems (CP) were regressed on a categorical variable indicating time since recent blunt smoking experience (Figure 4.3.2). Never blunt smokers were compared to mutually exclusive categories of those who smoked blunts within the past month ('past month'), smoked blunts more than 30 days ago but within the past year ('past year'), or more than 12 months ago ('prior use').

In an unadjusted model, any history of blunt smoking was associated with higher levels of CP, with larger estimates for more recent blunt use. For example, those who had smoked blunts within the past month had higher levels of CP than 'past-year' blunt smokers ($\beta$=0.98 vs. 0.62, respectively). Likewise, 'past-year' blunt smokers had higher levels of CP than 'prior users' ($\beta$=0.28). When the model adjusted for the influence of sex, age, race/ethnicity, or population density, estimates for blunt use recency did not appreciably change (Figure 4.3.3). Males, younger age groups, Hispanics, "Other" racial/ethnic groups, and residents of rural areas were associated with higher levels of CP. African-Americans/Blacks were no different than Whites on level of CP, nor were there differences observed between those living in more urban areas (CBSA $\geq$1 million vs. CBSA<1 million). The final model incorporated the influence of alcohol problems (AP) and tobacco dependence (TD) within the model. Estimates for blunt smoking recency did not change appreciably (Figure 4.3.4).

As a probe into the possibility that the relationship between CP and blunt smoking might differ by frequency of blunt smoking, the model was then re-estimated using days of blunt use in the past month, with a response range from zero to 30 days. There was a positive association such that for every added day of blunt smoking, there was a 0.03 increase along the dimension of CP (Figure 4.3.5). This estimate cannot be interpreted as an effect because temporal sequencing

and feedback loops have not been taken into account, notwithstanding a fundamental difference in the scales between count and categorical variables. In exploratory analyses, past-month blunt frequency was categorized (0 days; 1-7 days; 8-14 days; 15-21 days; 22-30 days), and results showed an estimated increase in effect size for each category as compared to those who did not use blunts in the past month: β=0.45 (1-7 days); β=0.59 (8-14 days); β=0.73 (15-21 days); β=0.84 (22-30 days) (data not shown in table or figure).

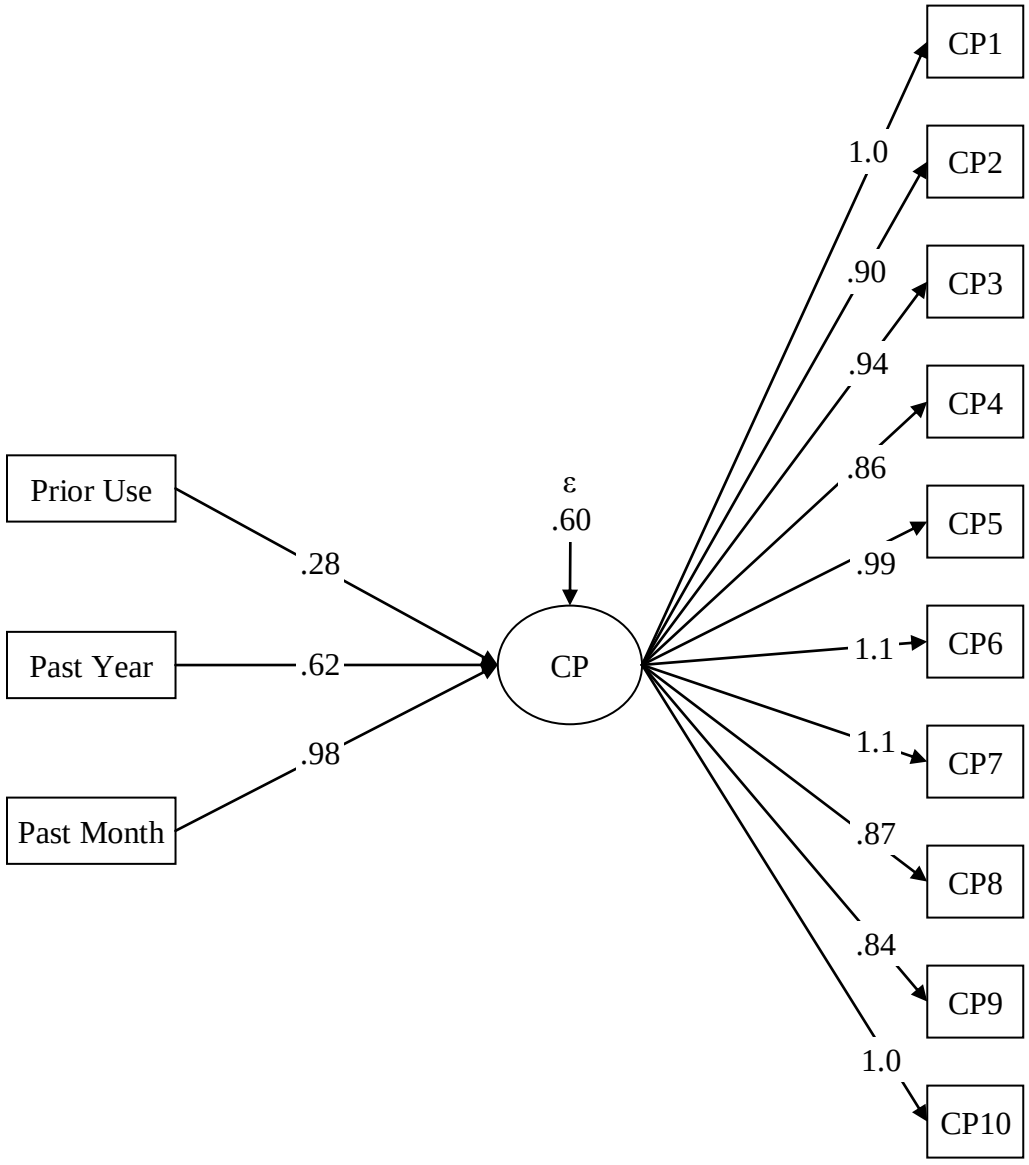


**Figure 4.3.2.** Association between level of cannabis problems (CP) and blunt smoking recency among past-year cannabis users (n=67,519). CFI=0.95; TLI=0.95; RMSEA=0.02.

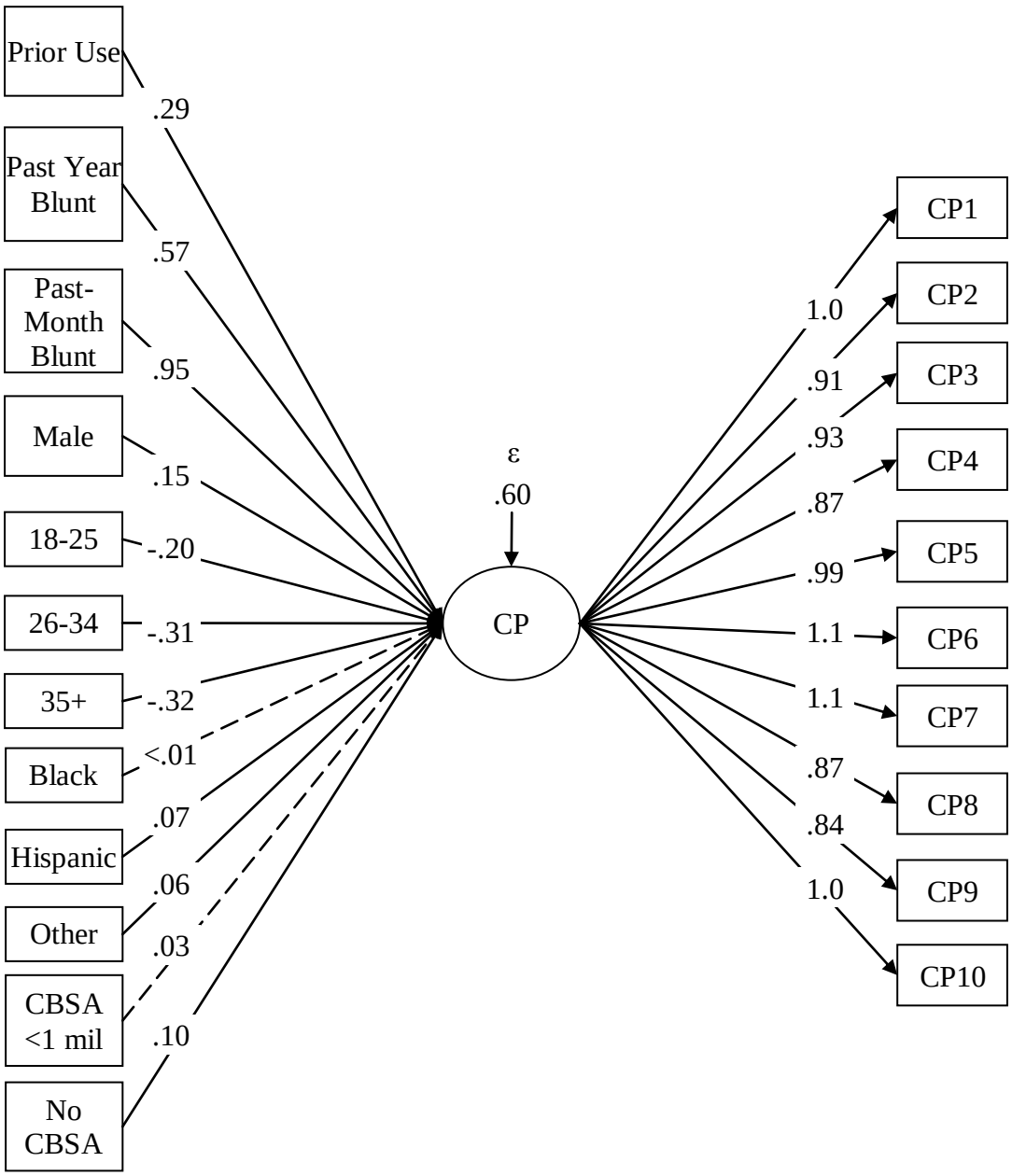



**Figure 4.3.3.** Association between cannabis problems (CP) and blunt use recency, sex, age, race/ethnicity, and population density (n=67,519). Note: Dashed lines indicate estimate with p>0.05. CFI=0.94; TLI=0.93; RMSEA=0.02.

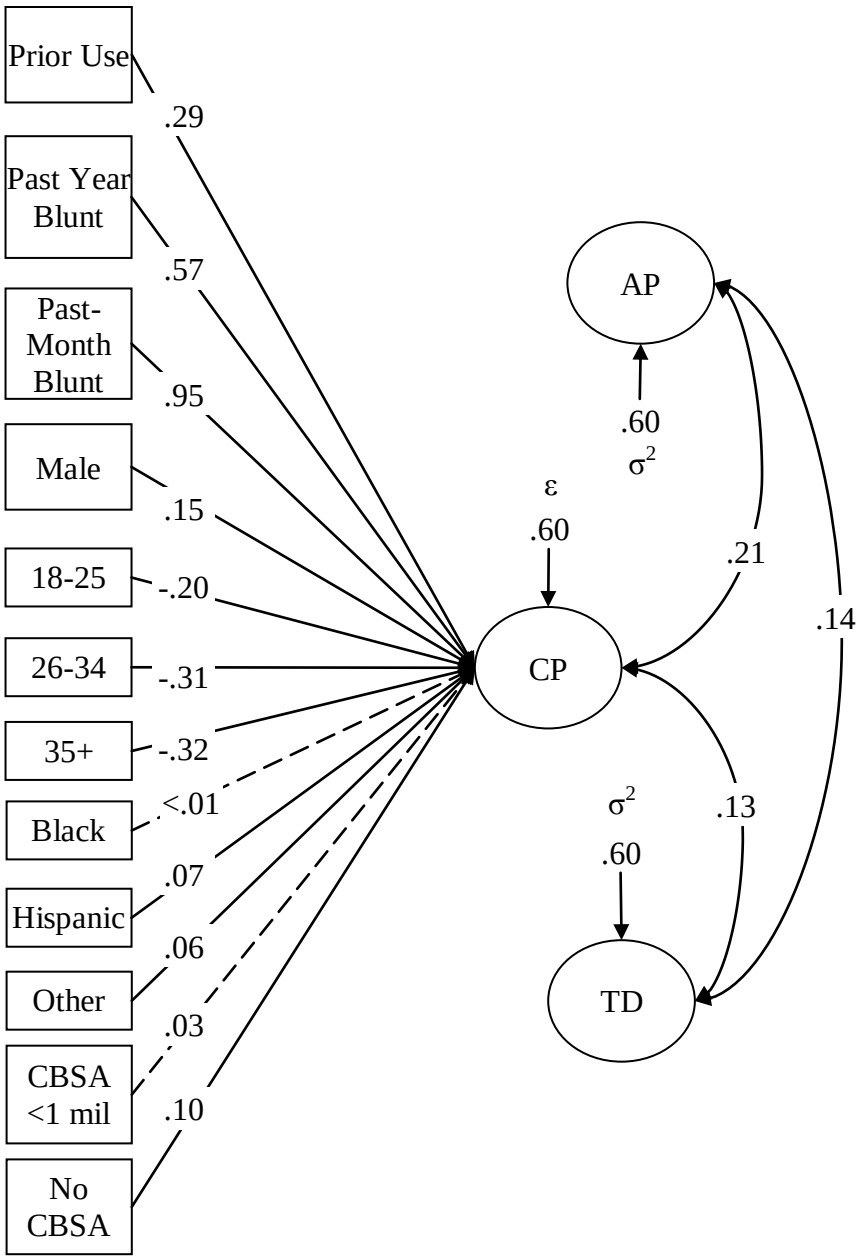



**Figure 4.3.4.** Association between cannabis problems (CP) and recent blunt use, background characteristics, alcohol problems (AP), and tobacco dependence (TD). Dashed lines indicate estimates with p>0.05. Latent structure and factor loadings not depicted for CP, AP, and TD in this figure. n=67,519; CFI=0.992; TLI=0.992; RMSEA=0.02.

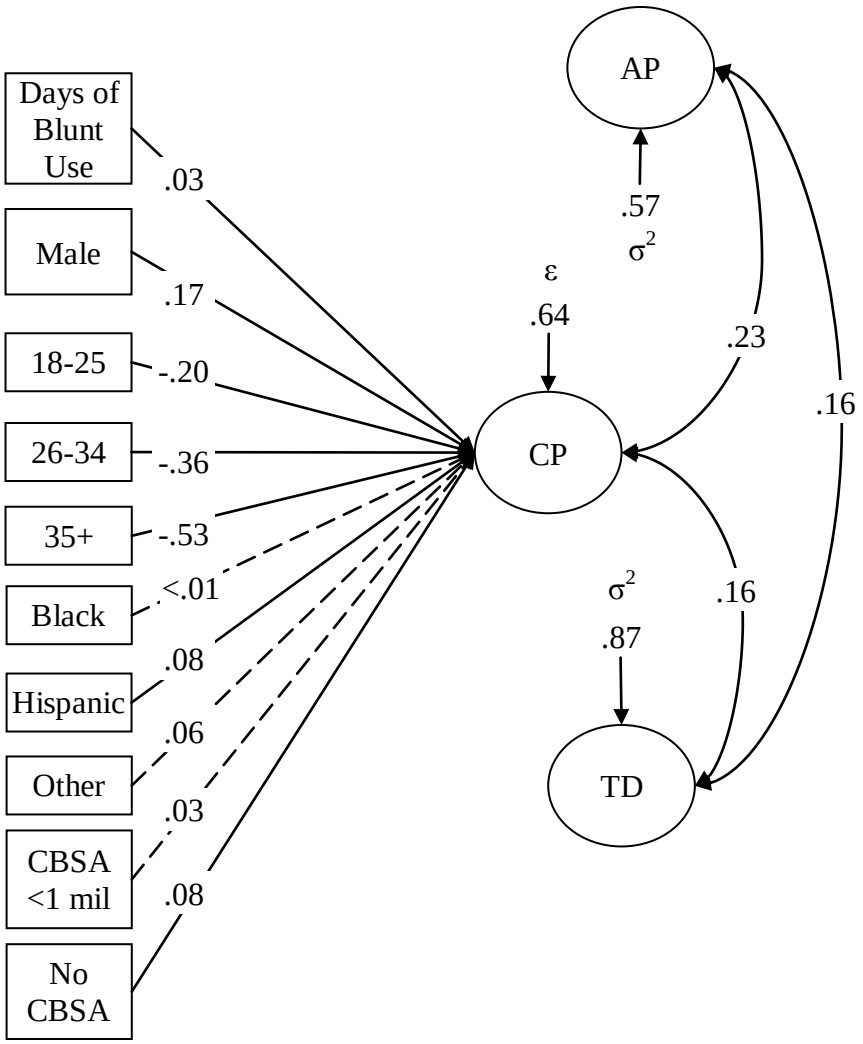



**Figure 4.3.5.** Association between cannabis problems (CP) and days of blunt use in the past month, background characteristics, alcohol problems (AP), and tobacco dependence (TD). Dashed lines indicate estimates with p>0.05. Latent structure and factor loadings not depicted for CP, AP, and TD in this figure. n=67,519; CFI=0.994; TLI=0.994; RMSEA=0.02.

### 4.4. Study 4: Time to Cannabis Onset and Cannabis Problems.

This study's aim was to estimate the degree to which early-onset cannabis smoking might affect risk of developing cannabis problems. The data are from the World Mental Health Surveys.

4.4.1. Frequency and Distribution of Cannabis-Only Users

Among 6,609 cannabis-only users in the sample, 80 (1.2%) had qualified as cases of cannabis dependence (CD) when assessed at WMHS baseline (Table 4.4.1). Eight WMH countries contributed no cases of CD among cannabis-only users, either because there were too few cannabis-only users, and/or CD was rare. Cannabis dependence was based on qualifying under either DSM-IV or ICD-10 criteria, with most CD cases qualified under both criteria (n=73). In addition, all but two respondents with CD had one or more features of socially maladaptive or hazardous cannabis use experiences (data not shown in table).

**Table 4.4.1.** Frequency of cannabis dependence (CD) among cannabis-only users by World Mental Health Survey site.

| Country | No | Yes | Total |
|---|---|---|---|
| Brazil | 245 | 4 | 249 |
| Colombia | 257 | 3 | 260 |
| Mexico | 210 | 2 | 212 |
| United States | 1,365 | 13 | 1,378 |
| Bulgaria | 14 | 0 | 14 |
| Northern Ireland | 208 | 2 | 210 |
| Romania | 16 | 0 | 16 |
| Iraq | 1 | 0 | 1 |
| Israel | 449 | 0 | 449 |
| Lebanon | 40 | 0 | 40 |
| Nigeria | 34 | 0 | 34 |
| Japan | 6 | 0 | 6 |
| China | 3 | 0 | 3 |
| New Zealand | 3,681 | 56 | 3,737 |
| **Total** | 6,529 | 80 | 6,609 |

Distribution of the cannabis-only sample by CD and other variables of interest are shown in Table 4.4.2. Mean age of first IRD opportunity was three years younger for those with CD compared to those without (15 vs. 18), and age of first cannabis use also differed by three years (17 vs. 20). Two-thirds of cannabis-only users have smoked tobacco cigarettes (66%) and 5.8% had alcohol dependence (AD).

**Table 4.4.2.** Distribution of Cannabis-Only Sample by Relevant Characteristics and Cannabis Dependence

| | | Cannabis-Only (n=6,609) | | Cannabis Dependence | | |
|---|---|---|---|---|---|---|
| **Variable** | **Category** | **Total** | **%** | **No (n=6,529)** | **Yes (n=80)** | **%Yes** |
| Age of 1st IRD Opportunity | (Mean) | 18 | - | 18 | 15 | - |
| Age of 1st Cannabis Use | (Mean) | 20 | - | 20 | 17 | - |
| Cigarette Smoking Status | Never/Only a few | 2,246 | 34.0 | 2,230 | 16 | 0.7 |
| | Ex-Smoker | 1,752 | 26.5 | 1,728 | 24 | 1.4 |
| | Current Smoker | 2,610 | 39.5 | 2,570 | 40 | 1.5 |
| | Missing | 1 | 0.0 | 1 | 0 | 0.0 |
| Alcohol Dependence | No Dependence | 6,223 | 94.2 | 6,187 | 36 | 0.6 |
| | Dependence | 386 | 5.8 | 346 | 40 | 10.4 |
| Sex | Female | 3,246 | 49.1 | 3,213 | 33 | 1.0 |
| | Male | 3,363 | 50.9 | 3,316 | 47 | 1.4 |
| Age | (Mean) | 37 | - | 37 | 32 | - |
| Income | Low | 1,371 | 20.7 | 1,331 | 40 | 2.9 |
| | Low-Average | 1,780 | 26.9 | 1,758 | 22 | 1.2 |
| | Above Average | 3,175 | 48.0 | 3,158 | 17 | 0.5 |
| | Missing | 283 | 4.3 | 282 | 1 | 0.4 |
| Education | < Secondary | 2,240 | 33.9 | 2,193 | 47 | 2.1 |
| | Secondary | 4,369 | 66.1 | 4,336 | 33 | 0.8 |
| Employment | Not-Working[a] | 1,508 | 22.8 | 1,478 | 30 | 2.0 |
| | Working | 5,101 | 77.2 | 5,051 | 50 | 1.0 |
| Marital Status | Never married | 3,814 | 57.7 | 3,773 | 41 | 1.1 |
| | Previously married | 897 | 13.6 | 887 | 10 | 1.1 |
| | Married-cohabiting | 1,897 | 28.7 | 1,868 | 29 | 1.5 |
| | Missing | 1 | 0.0 | 1 | 0 | 0.0 |

**Table 4.2.2.** (cont'd)

| | | | | | | |
|---|---|---|---|---|---|---|
| Parent's Highest Level of Education | Primary or less | 989 | 15.0 | 969 | 20 | 2.0 |
| | Secondary | 3,098 | 46.9 | 3,060 | 38 | 1.2 |
| | Tertiary | 1,978 | 29.9 | 1,960 | 18 | 0.9 |
| | Missing | 544 | 8.2 | 540 | 4 | 0.7 |
| Major Depressive Episode | No Depression | 5,049 | 76.4 | 4,994 | 55 | 1.1 |
| | Depression | 1,560 | 23.6 | 1,535 | 25 | 1.6 |

[a] Not-working category: students, homemakers, retired, and other non-employed.

The distribution of the time to cannabis onset (TCO) variable, operationally defined as the number of years between age of first IRD opportunity and age of first cannabis use, was examined using histogram plots (Figure 4.4.1). Nearly half of cannabis-only users (47%) had an opportunity to try drugs and used cannabis for the first time at the same age. Another third (32%) used cannabis within the three years after their first drug opportunity. The histogram plot also revealed that some respondents had negative values due to reporting a younger age of cannabis onset than IRD opportunity (n=185; 2.8%). Figure 4.4.2 shows the same distribution of TCO when observations with negative values were removed.

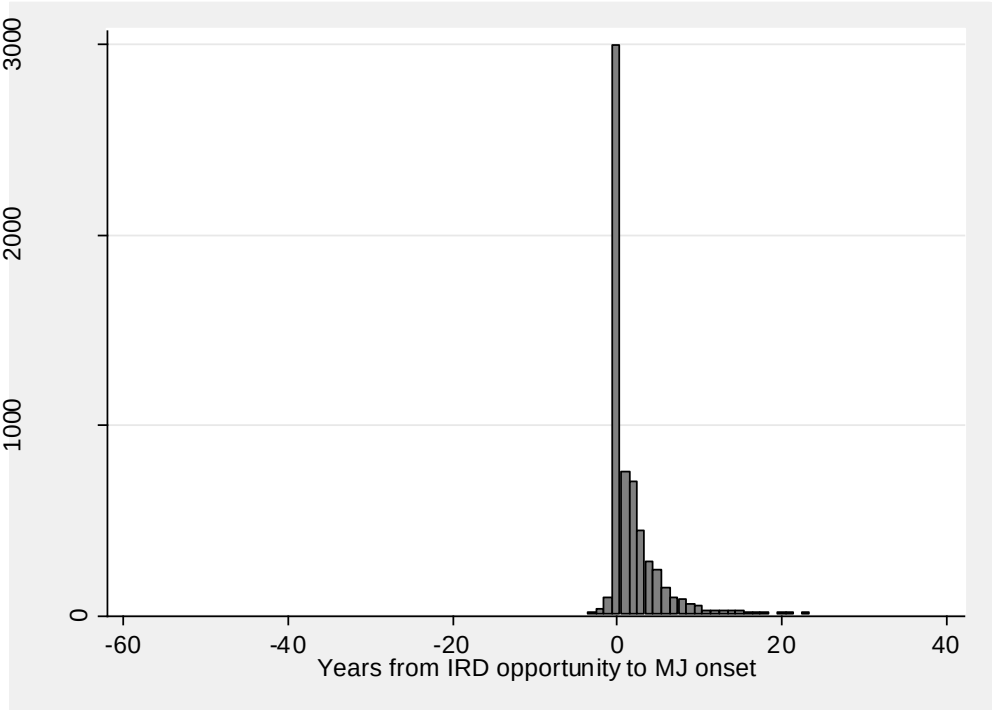



**Figure 4.4.1.** Histogram plot of time to cannabis onset (TCO), all values.

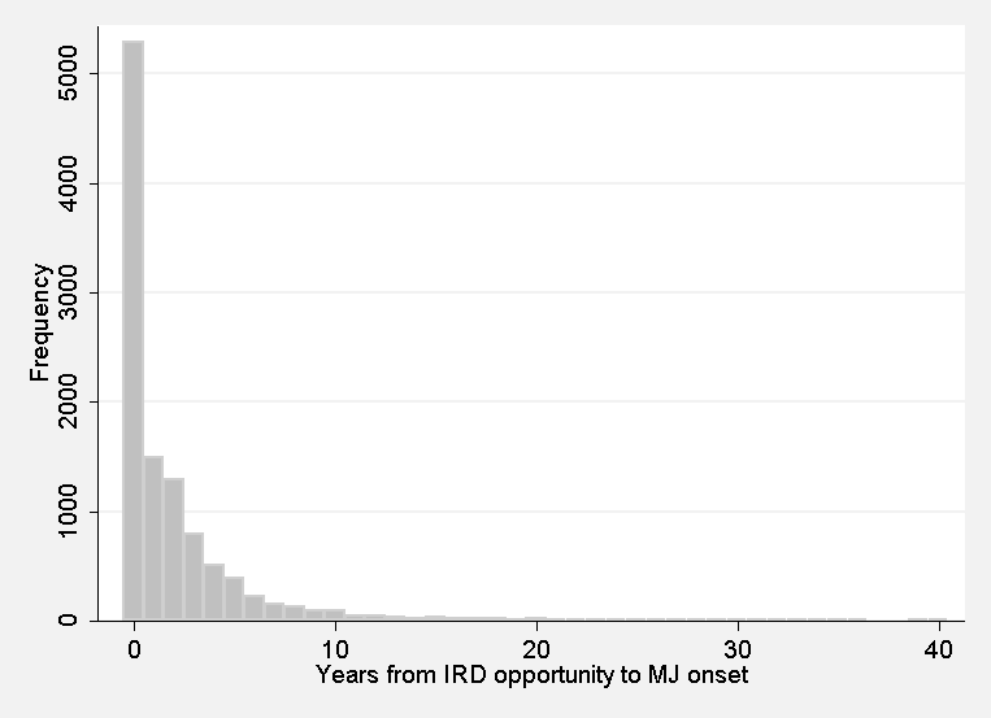



**Figure 4.4.2.** Histogram plot of time to cannabis onset (TCO) for non-negative values.

4.4.2. Cannabis Dependence (CD) and Time to Cannabis Onset (TCO)

We use SLT as an abbreviation for a short lag time from first chance to try cannabis to actual use of cannabis, and TCO to refer to time elapsed from cannabis onset until onset of cannabis use. In the initial logistic regression model, SLT was inversely associated with odds of developing cannabis dependence after adjusting for age of first IRD opportunity (β=-0.2; 95% CI = -0.3, -0.1; p<0.001; Table 4.4.3). This means that for every year increase in TCO, there was about a 20% *decrease* in the odds of experiencing cannabis dependence. Additional models controlled for the influence of country, sex, age, income, education, employment, marital status, parent's education, and major depression. No difference in the estimate between CD and TCO was found in these models. A smaller sample size in Models 2 and 3 versus Model 1 was due to some countries having too few cannabis-only subjects for multivariable analysis. Thus, Models 2 and 3 were based on data from Colombia, Mexico, New Zealand, Brazil, Northern Ireland, and the United States, which had sufficient numbers of cannabis-only users. Estimates were no different in Model 1 if restricted to the same sample used for Model 3 (data not shown in table).

**Table 4.4.3.** Unadjusted and covariate adjusted estimates of the association between cannabis dependence (CD) and time to cannabis onset (TCO) use among cannabis-only users.

| Model | n | β | 95% CI | | P-value |
|---|---|---|---|---|---|
| Model 1 | 6,074 | -0.2 | -0.3 | -0.1 | <0.001 |
| Adjusted for age of first IRD opportunity. | | | | | |
| Model 2 | 5,512 | -0.2 | -0.3 | -0.07 | 0.001 |
| Adjusted for Model 1 covariate, country, sex, and age. | | | | | |
| Model 3 | 5,512 | -0.2 | -0.3 | -0.06 | 0.004 |
| Adjusted for Model 2 covariates, smoking, income, education, employment, marital status, parent's education, major depression. | | | | | |

4.4.3. Association Between Cannabis Problems (CP) and Time to Cannabis Onset (TCO)

Factor analysis was conducted using the eight manifest items for cannabis dependence (CP0-CP7) and four items characterized as socially maladaptive or hazardous (CP8-CP11). A single latent factor was observed (Figure 4.4.3). This model fit the data well (CFI= 0.999; TLI= 0.999; RMSEA=0.009). An inverse association was observed ($\beta$=-0.05; $p<0.001$) when level of CP was regressed on TCO alone (Figure 4.4.4). Adding statistical control for age of first IRD opportunity, country, sex did not appreciably change the point estimate for TCO (Figure 4.4.5; $\beta$=-0.08; $p<0.001$). This model also revealed that males had a higher level of CP ($\beta$=0.31), while age and age of first IRD opportunity were inversely related to CP ($\beta$=-0.01 and -0.07, respectively). The final model depicted (Figure 4.4.6) controlled in the model for additional drug influences (i.e., cigarette smoking and a latent factor of alcohol problems), background characteristics (i.e., income, education, employment, marital status, and parent's education), and presence of lifetime occurrence of major depressive episode (MDE). The latent factor structure of alcohol problems (AP) used in the model is shown in Figure 4.4.7. Despite possible model misspecification concerning some covariates (that is, the level of CP could potentially be a determinant of income, educational attainment, or marital status), the relationship between CP and TOC remained relatively unchanged ($\beta$=-0.07).

In addition, the data exploration disclosed positive relationships between level of CP and level of AP ($\beta$=0.53), being a current or ex-cigarette smoker versus never smoking ($\beta$=0.48 and 0.56, respectively), having been previously married versus never married ($\beta$=0.27), and lifetime MDE ($\beta$=0.38). Finishing secondary school (compared to only finishing primary school) and having a parent with at least a secondary school education (versus primary) were associated with lower levels of CP. Having a higher income, being currently married, and having parents with a

higher level of education appeared to have no influence over level of CP. There was no consistent relationship between a specific WMH country and level of cannabis problems across models.

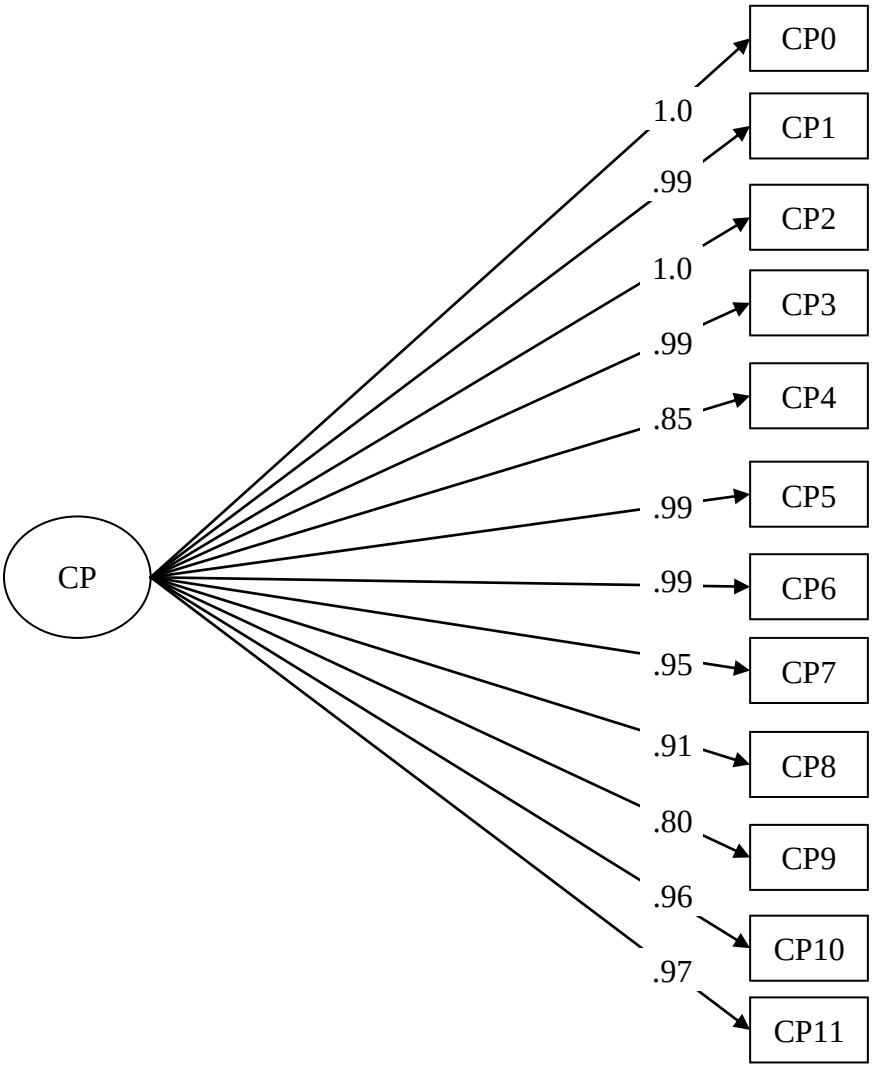



**Figure 4.4.3.** Measurement model of cannabis problems (CP). n=6,609; CFI= 0.999; TLI= 0.999; RMSEA=0.009.

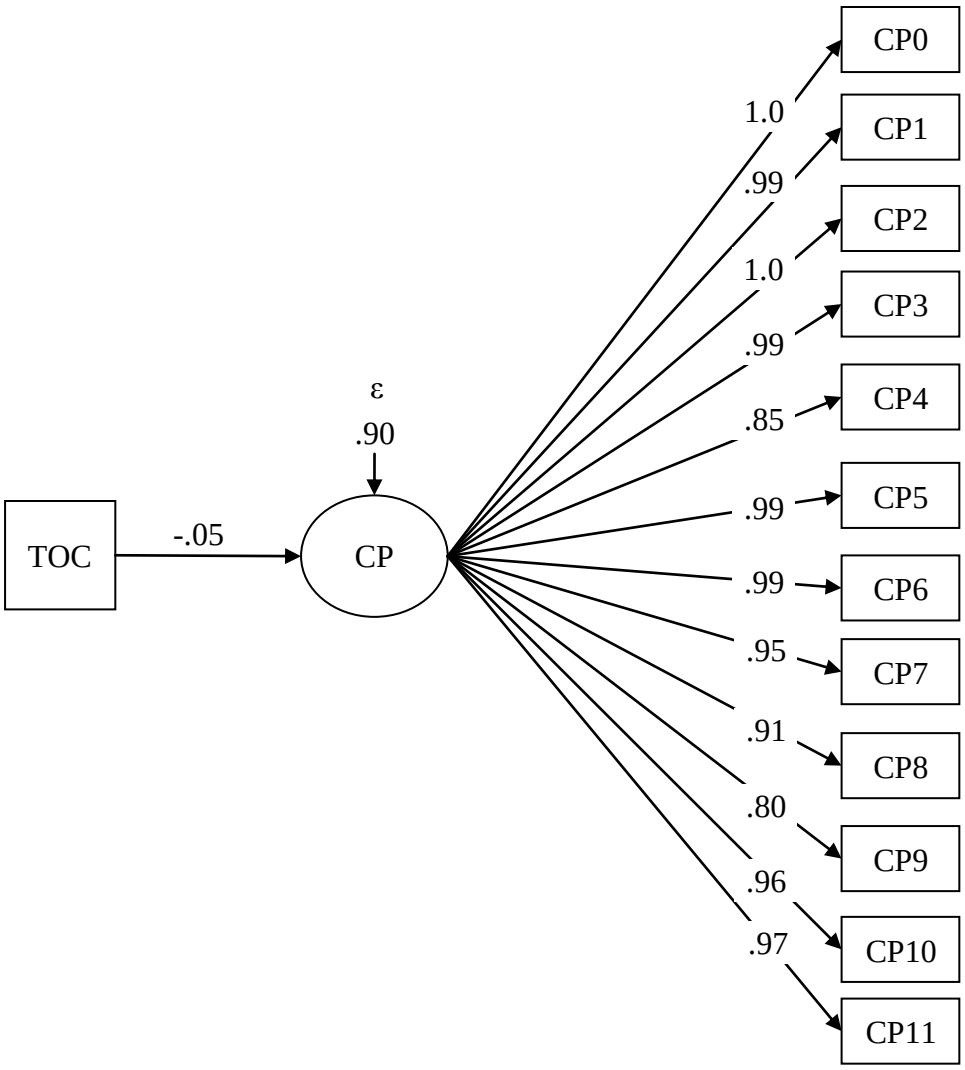



**Figure 4.4.4.** Unadjusted association between cannabis problems (CP) and time to cannabis onset (TOC). n=6,081; CFI=0.998; TLI=0.998; RMSEA=0.011.

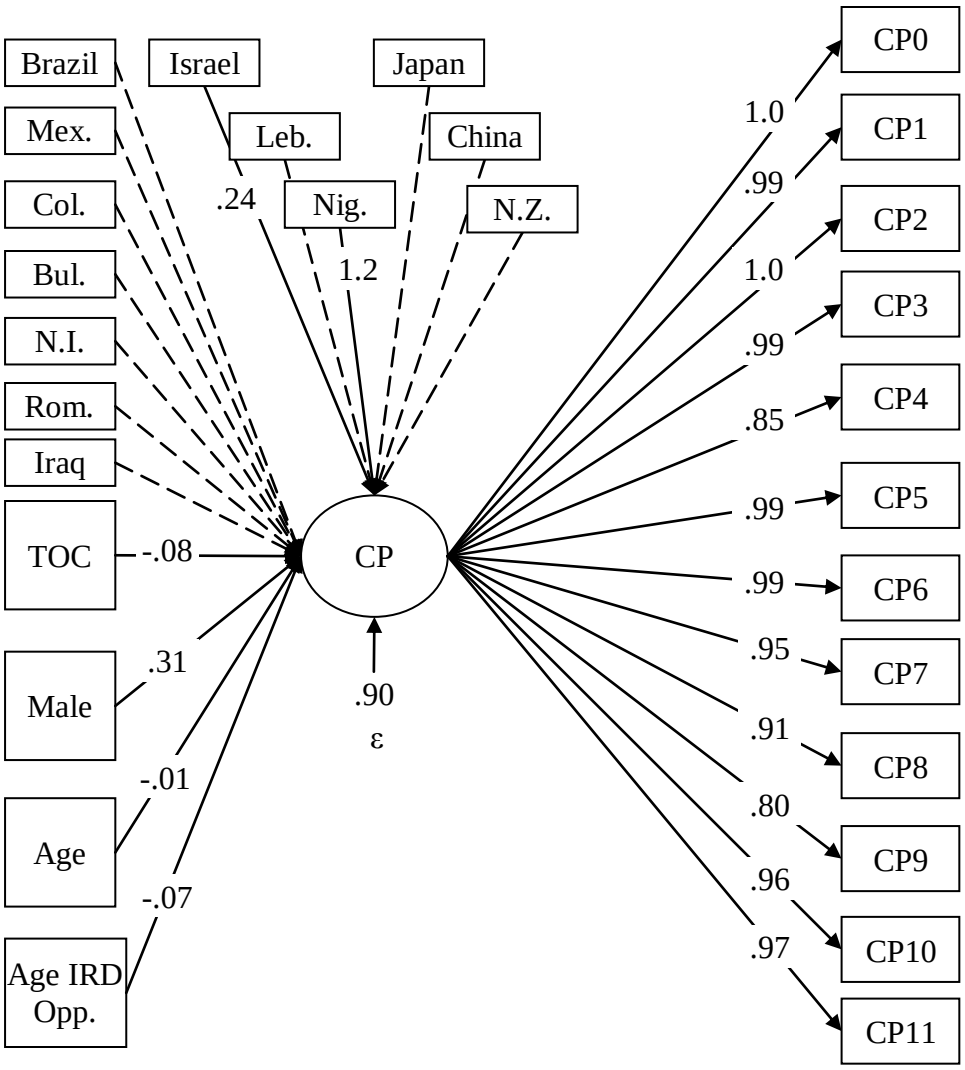



**Figure 4.4.5.** Association between cannabis problems (CP), time to cannabis onset (TOC), country, sex, and age. Dashed lines indicate p-values greater than 0.05, point estimates not shown. n=6,030; CFI=0.997; TLI=0.996; RMSEA=0.009.

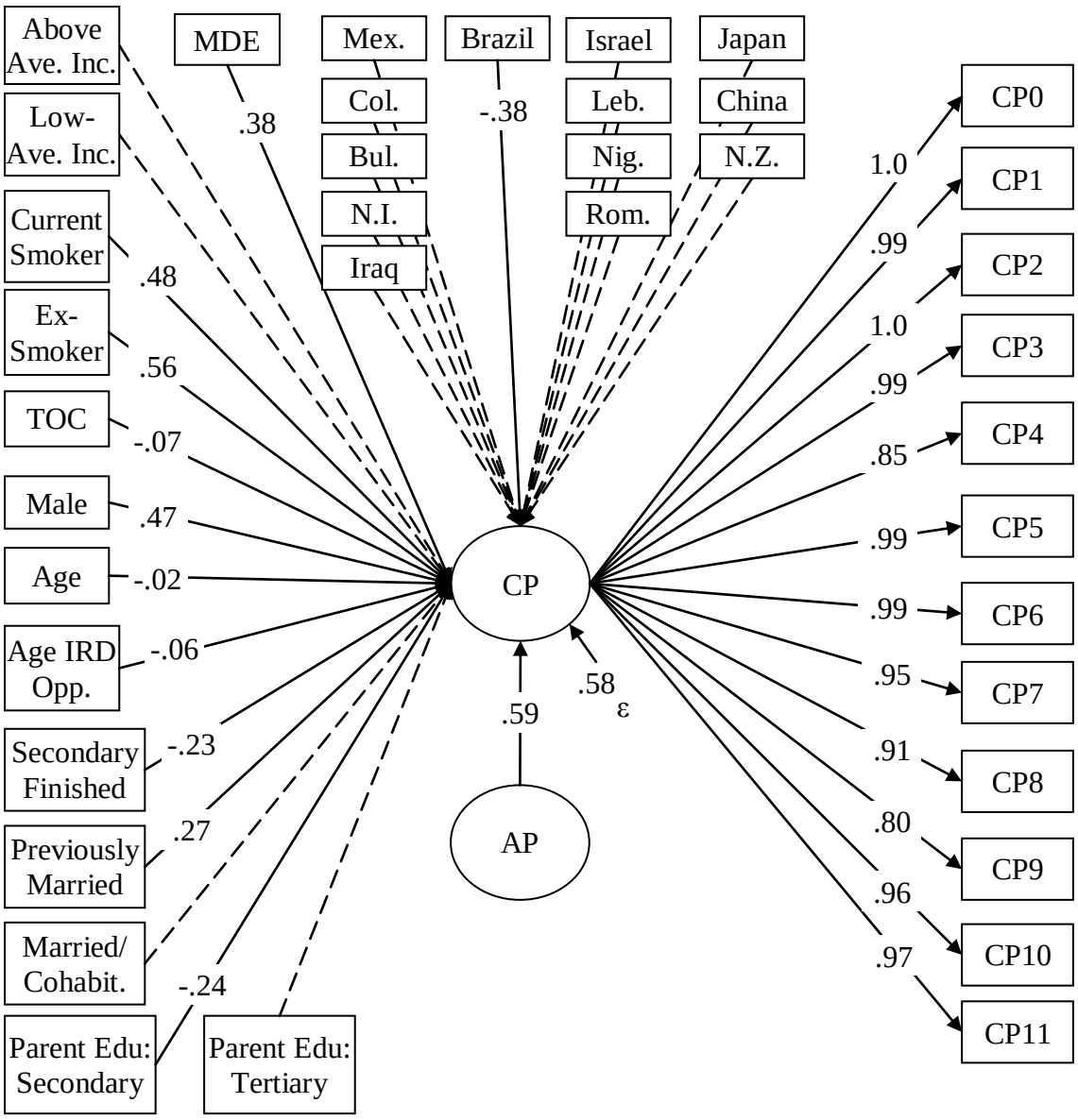



**Figure 4.4.6.** Association between cannabis problems (CP) and time to cannabis onset (TOC) adjusting for age of first IRD opportunity, cigarette smoking, alcohol problems (AP), country, major depressive episode (MDE), and other background influences. Latent structure and factor loading estimates for AP not depicted in this figure. Dashed lines indicate estimates with p-values greater than 0.05, with these estimates not depicted. n=6,030; CFI=0.987; TLI=0.986; RMSEA=0.02.

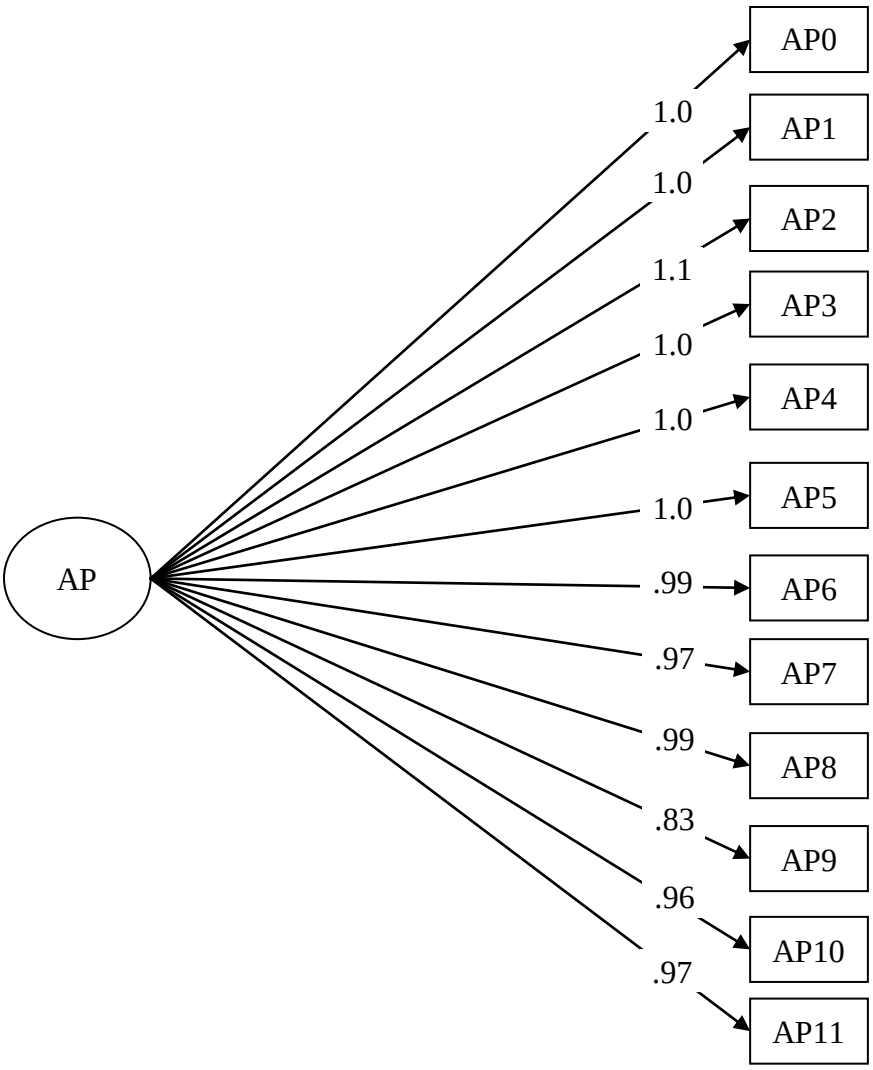



**Figure 4.4.7.** Measurement model of alcohol problems (AP) with factor loadings from model depicted in Figure 4.4.6.

# CHAPTER 5. DISCUSSION

This final chapter presents a discussion of the main findings and results of each study herein. In this discussion, one of my goals is to interpret the results within the context of existing knowledge, including the prior literature and underlying theoretical concepts, as introduced in the background chapter. In addition, I wish to be open to each study's limitations, a malady which no scientific research is immune, but also highlight what I think to be the research's many strengths. In the final chapter (Chapter 6), I discuss what can be concluded from the research, particularly any implications for future research and possibly for public health practice.

## 5.1. Study 1: Early-Onset Cannabis Smoking and Depression Spells

As has been previously mentioned, the research for Study 1 has already been published at the time of completing this dissertation. Thus, the discussion that follows is largely reproduced here with appropriate updated information since publication. For the most part, the material in Section 5.1 qualifies as an extended quotation of the previously cited source material (Fairman & Anthony, 2012).

In this study, the primary research aim was to estimate the degree to which early-onset cannabis smoking initiated prior to age 18 years might signal an increased risk of a later adult-onset incident depression spell. No more than a modest excess odds for this relationship was found in the comparison of early-onset users with individuals who had never smoked cannabis. This association remained statistically robust after covariate adjustment for elapsed time of cannabis involvement, onset of tobacco cigarettes and alcohol, sex, age, and race/ethnicity, consistent with prior studies predicting a modest association between various forms of adolescent cannabis use and later depression in adolescence or young adulthood (D. W. Brook, Brook,

Zhang, Cohen, & Whiteman, 2002; Fergusson et al., 2002; B. E. Green & Ritter, 2000; Groth & Morrison-Beedy, 2010; Hayatbakhsh et al., 2007; Pahl et al., 2010; Patton et al., 2002; Rey et al., 2002). Our study's results add to the literature on the association between cannabis and depression by extending the timeline to include the first occurrence of a sustained spell of depression in age groups past adolescence. This refinement was made possible via a constraint on the temporal sequencing of first cannabis use and depression spell, made possible by using age-of-onset data. However, for completeness, several studies with null results should be noted, in which original unadjusted associations were rendered null once potential confounders were taken into account, much as the associations under study here were much-attenuated with statistical adjustments for covariates of interest (de Graaf et al., 2010; Degenhardt et al., 2010; Fergusson & Horwood, 1997; Griffith-Lendering et al., 2011; Lynskey et al., 2004; Pedersen, 2008; Windle & Wiesner, 2004).

As mentioned elsewhere (Fairman & Anthony, 2012), readers may interpret the overall population estimate as too modest to sustain a causal inference due to uncontrolled sources of potential confounding, such as a diathesis that might determine both EOCU and adult-onset depression spells. For example, de Graaf and colleagues (2010) suggested that early behavioral dysregulation or conduct problems might be one such indication of a shared diathesis. If controlled, these now-omitted background characteristics might well render the association null, as in de Graaf et al. (2010). Whereas the present study included no measures of early behavioral or conduct problems, Greenland and O'Rouke (2008) provide an approach that can be used to gauge whether (and by how much) an association might shift toward the null if an unmeasured covariate had been controlled. Their method is based upon the ratio of adjusted and unadjusted estimates as derived from prior research. To illustrate, according to estimates reported by de

Graaf et al. (2010), the ratio of adjusted to unadjusted OR estimates is 0.9. As forecast by the Greenland-O'Rourke method, multiplication of 0.9 times the present study's point estimate of 1.7 yields an odds ratio estimate of 1.5 (i.e., closer to the null). Accordingly, this study's conclusion continues to be that the link from early-onset cannabis smoking to later adult-onset of a depression spell is quite modest (but is non-null).

This study's secondary research question was whether the estimated associations with depression spell might be different when studied in association with adult-onset cannabis smoking. In this study's estimates, little difference between the early-onset and adult-onset subgroups of cannabis smoking onset was found with respect to occurrence of adult-onset depression spells in models with covariate adjustment for potential confounders and background characteristics. One might expect that the delay of cannabis onset until adulthood might have a diminished effect on the incidence of depression spells, in congruence with theories of either a direct influence of exogenous cannabinoids on the maturing adolescent brain (Rice & Barone, 2000; Schneider, 2008), or an indirect influence through difficulty in assuming adult roles that lead to depression (B. E. Green & Ritter, 2000; Kandel et al., 1986; Marmorstein & Iacono, 2011). Nonetheless, the study findings cannot be said to support these theoretical formulations of the cannabis-depression associations. In addition, one might also expect the effect of EOCU to be greater and more pronounced when cannabis smoking has started very very early in late childhood or early adolescence, as compared to associations found when cannabis smoking has started in later adolescence. However, in analyses that separated early-onset cannabis smoking into year-by-year age categories, there was no strong support for any age-related gradient in the strength of association after statistical adjustment. As such, early-onset cannabis smoking might merely be a marker for more regular, chronic use in adulthood. For example, Georgiades and

Boyle (2007) found that cannabis use in adolescence only (but not in adulthood) had little association with depression, but that occurrence of depression was associated with cannabis use in adolescence and continued into adulthood, as well as with adult-onset cannabis smoking without adolescent use of cannabis.

The effect of early-onset cannabis use on later depression spells, if there is any, might be mediated through the influence of adolescent cannabis use on psychosocial factors associated with depression. Most of the variables that were considered individually - educational attainment, employment status, total family income, marital status, number of times married, ever been arrested, population density - had little apparent effect on the early-onset cannabis-associated odds of depression spells. Only having ever used other illegal drugs besides cannabis produced a noteworthy, but not full attenuation of the originally observed EOCU-depression spell association. Statistical control of all considered covariates in a single model rendered the EOCU-depression spell null, but only in the presence of illegal drug use, which might mediate the association, and years of cannabis involvement, which showed to be highly correlated with age of cannabis onset. Thus, the study findings are more consistent with a recent report that concluded the increased risk of later depression for those with an adolescent-onset cannabis use disorder was no more than partially mediated by adverse psychosocial consequences such as educational failure, unemployment, and criminal behavior (Marmorstein & Iacono, 2011). This recent work can be contrasted with earlier findings of others emphasizing the meditational role of these factors (B. E. Green & Ritter, 2000; Kandel et al., 1986). Of course, it should be noted that there is at least one limitation to our approach: since these variables were assessed as of the time of the interview, it is possible that these variables do not fall within the causal chain – e.g., they could be a result of depressed mood, rather than a cause.

Early-onset tobacco or alcohol use was also associated with an excess odds of a later depression spell. The strength of the association was very modest for early tobacco cigarette smoking, but about two-fold for early alcohol drinking. Adjustment for cannabis and alcohol use, in theory, might attenuate estimates of the effect of early-onset tobacco cigarette use, which typically has an earlier onset than other drugs (Degenhardt et al., 2008). A related rationale might be used to explain the finding that adult-onset tobacco cigarette smoking was not associated with depression spells. For alcohol drinking, both early- and adult-onset drinking were positively associated with depression spells, but the odds ratio based on early-onset drinkers were slightly greater and statistically different than the odds ratio estimates based on adult-onset drinkers. While speculative, the pattern of findings might prompt a suggestion that it could be possible to attempt prevention or delay of the onset of alcohol drinking, which in turn might have an impact on occurrence of later mood disturbances. However, our aim was not to test this relationship, and we should point out that our conceptual model did not account for lifetime cumulative exposure of tobacco or alcohol, such as with elapsed time of cannabis involvement, which might explain these findings. Recent reviews by Chaiton et al. (2009) and Boden and Fergusson (2011) draw conclusions in favor of causal relationships that link tobacco smoking or alcohol drinking with physical health, and also with depression.

This research should be viewed in light of several additional limitations, as noted below. First, the NSDUH collects little information on the childhood experiences of adult respondents at the time of interview. As a consequence, some potential confounders of the cannabis-depression association, such as a history of childhood conduct problems, early family dysfunction, or other mental disorders likely to have their onset in childhood/adolescence were not measured and therefore are omitted variables (Degenhardt et al., 2003). As illustrated using the Greenland-

O'Rourke method, covariate adjustment most likely implies attenuated and perhaps null cannabis-depression associations due to the omission of these potentially confounding variables in the NSDUH measurement plan. Second, difficulties in recall or reporting of the age of onset of cannabis use or depression spell sometimes can occur, although in this sample there often were large differences in the age-of-onset of cannabis smoking in relation to age-of-onset of depression spells, which implies that roughly accurate age-of-onset values should suffice in this context. Third, the link from cannabis to depression might unfold within a matter of weeks or months after adolescent onset of cannabis smoking. If so, a research design with week-to-week or month-to-month time sequence granularity would be required to disclose any palpable association under these circumstances, and the case-crossover design might be needed (e.g., see O'Brien et al. 2005). This specific limitation does not undermine the value of the study estimates just reported, which are based on a prevailing view that early-onset cannabis use might be a signal of later incident depression spells occurring well after the interval of cannabis intoxication (e.g., Chen et al. 2002).

Some strengths of this research include having large sample sizes that yield statistically precise estimates even when modest-level associations are observed, plus the strengths of a nationally representative sample that helps to promote the external validity of these results, as well as standardized computer-assisted assessment methods to maximize validity and reliability of the study measurements. That is, computer-assisted self-interviewing methods may have helped ensure more honest, more complete, and perhaps more accurate responses to questions on sensitive topics such as drug use and mood disturbances such as depression spells. These are important strengths in a cross-sectional survey that is unburdened by the uncertainties that come with sample attrition during longitudinal follow-up studies on relationships of this type, which

otherwise might be said to yield important evidence on a cannabis-depression association of public health significance.

To conclude with an honest appraisal of the present findings, the accumulated evidence, and their implications, mention must be made of a prominent assumption of all current observational research on the suspected hazards associated with early-onset drug use, including cannabis smoking. The rest of this concluding statement is offered with a spirit of mind prompted by Professor C.F. Manski's description of a general problem in human behavioral and social science research of an observational character. Namely, Manski has noted that in these research areas we often fail "... to face up to the difficulty of [the] enterprise. Researchers sometimes do not recognize that the interpretation of data requires assumptions. Researchers sometimes understand the logic of scientific inference but ignore it when reporting their own work. The scientific community rewards those who produce strong novel findings. The public, impatient for solutions to its pressing concerns, rewards those who offer simple analyses leading to unequivocal policy recommendations. These incentives make it tempting for researchers to maintain assumptions far stronger than they can persuasively defend, in order to draw strong conclusions" (Manski, 1999).

Accordingly, readers of this work deserve to appreciate a crucial assumption, if the goal is to evaluate the current evidence and judge that the prevalence of adult-onset depression spells might be reduced by preventing or delaying onset of cannabis smoking. Namely, as outlined elsewhere (Anthony, 2013; O'Brien, Comment, Liang, & Anthony, 2012), the crucial assumption is the 'no omitted variables' assumption in relation to this study's model specifications. Here, there must be a strong assumption that there is no set of background variables, lurking behind the scenes, either unknown or unmeasured or ineptly measured, that

might be functioning as a common vulnerability trait, accounting for both (a) an occasion of adolescent-onset cannabis smoking before age 18 years, and (b) an adult-onset depression spell after the 18th birthday. If there is an omitted variable, such as a gene that manifests its influence in the form of a simple pleiotropism, as might be the case with a genetic mutation that gives rise to an excess risk of both early-onset cannabis smoking and a later-onset depression spell, then it might be controlled in a behavioral genetics research design (e.g., with monozygotic twins). Nevertheless, if one suspects epigenesis or other forms of gene-environment interaction as a common substrate, then a subject-as-own-control (SAOC) type design would be required, and regrettably the primary SAOC design for large sample research is the epidemiologic case-crossover design -- which has little utility when there is a long induction interval from suspected causal exposure to later excess risk (O'Brien et al., 2012).

Accordingly, in the next step toward confirmation of the suspected cannabis-depression causal association, it might be best to turn attention toward randomized prevention trial evidence, where an early drug use prevention program has prevented or delayed the adolescent-onset of cannabis smoking. With a follow-up of adolescent prevention program participants into the adult years, there might be evidence of a linked reduction in the form of later reduced risk of the depression spells among those who responded well to the drug prevention program. A less compelling alternative design might involve a prospective follow-up of adolescent-onset cannabis smokers, stratified by whether initial cannabis smoking persisted and for how long it persisted, with an expectation that there might be reduced risk of the depression spell among adolescents who tried cannabis just once or twice and never again, or possibly a gradient of increasing risk across strata defined by length of persistent cannabis smoking in adolescence. Here again, the 'no omitted variables' assumption would surface, in that the earlier vulnerability

to reinforcing effects of cannabis smoking (with subsequent persistence of cannabis use) might also be a cause or marker of later vulnerability for a depression spell. It is for this reason that the follow-up of adolescent participants in randomized prevention experiments might be judged to be a more compelling next step in this line of research.

### 5.2. Study 2: Cannabis Problems and Functional Impairment Attributed to Recently Active Depression Spells

My aim for this study was to estimate the association between functional impairment attributed to depression and the level of problematic cannabis use in a representative sample of persons with depression in the past year. The guiding hypothesis was that persons experiencing more cannabis problems would have a higher level of depression-related functional impairment – a hypothesis that was motivated by the prior literature on the suspected causal relationship between cannabis and depression. Findings from this study show a positive relationship between cannabis problems and functional impairment attributed to depression. This association persisted after accounting for the influence of sex, age, race/ethnicity, alcohol problems, and tobacco dependence. Constraining the temporal sequencing between onset of cannabis use and onset of first depression spell did not alter the results. This result mitigated some of the concern that these findings could due to the 'self-medication' hypothesis, which has not been greatly supported by the prior literature (Hofstra, van der Ende, & Verhulst, 2002; Kandel & Chen, 2000; Kandel & Davies, 1986; Miller-Johnson, Lochman, Coie, Terry, & Hyman, 1998; Mueser et al., 1998; Weissman et al., 1999).

Few studies illuminate the relationships linking cannabis smoking, depression, and functional impairment, but results detailed in this research are consistent with what has been

published. For example, a recent study showed cannabis involvement was an independent predictor of functional impairment among a clinical sample of youths seeking treatment for a primary mood or anxiety disorder (Osuch et al., 2013). Another study following a sample of college students found trajectories of increased, late onset, or chronic cannabis use during college predicted higher depression scores and more days of impairment due to emotions (Caldeira et al., 2012). Several studies are informative, but more equivocal. For instance, Roberts and colleagues (2007) reported that in unadjusted models, cannabis dependence and abuse were both associated with having a mood disorder, but only abuse was associated with more impairment. Adjusted models did not have sufficient numbers to produce stable estimates. Meanwhile, Flisher and others (2000) observed that cannabis smoking included in a scale of risk behaviors (which also included cigarette smoking, alcohol use, sexual intercourse, violence, and suicide) was independently associated with having a mood disorder and greater functional impairment. However, over 20 risk factors were evaluated, and there was no indication of correction for multiple comparisons, so there is the possibility their findings may have been due to chance. One potentially contrasting finding was reported in a clinical sample of patients who had recently experienced a manic episode (Goetz et al., 2007). The authors found that other drug use, but not cannabis or alcohol, was associated with greater occupational impairment.

The current study in the dissertation research program assumed that the functional impairment experience can be attributed to depression, and that the relationship with cannabis problems is hypothesized to act through its influence on depressed mood. However, an alternative explanation of these findings could be that the functional impairment experienced (or part thereof) may be due to the experience of cannabis problems themselves, which are then possibly misattributed to depressed mood. Like major depressive episode (MDE), clinically

significant impairment or distress is defined as part of the diagnosis of cannabis dependence in the DSM-IV (American Psychiatric Association, 1994). Cannabis withdrawal is associated with a clinically significant degree of distress and impairment, and predicts higher levels of cannabis use after relapse (Allsop et al., 2012; Hasin et al., 2008). Thus, there is the potential for the 'chicken and egg problem' (which came first?), as well as the possibility of feedback mechanisms that drive both levels of cannabis problems and functional impairment.

Another notable finding was the stronger relationship between the level of tobacco dependence (TD) and functional impairment attributed to depression, as compared to level of cannabis problems. Unlike the situation with cannabis, tobacco smoking itself seems unlikely to directly produce much functional impairment, as many individuals are capable of being regular smokers without much detrimental effect on occupational or interpersonal roles. Nonetheless, this finding would be consistent with prior evidence that tobacco smokers are at an increased risk for depression, and thus might experience more functional impairment attributed to depression (Breslau, Peterson, Schultz, Chilcoat, & Andreski, 1998). Alternatively, tobacco smoking inhibits monoamine oxidase A in pre-clinical and clinical samples similar to the action of many antidepressants. It can be speculated that any observed higher level of tobacco consumption (and dependence) might have post-dated the onset of depression, contrary to the hypothesized direction in this investigation, and raising the chicken-egg problem (Fowler, Logan, Wang, & Volkow, 2003).

To my knowledge, this is the first study to investigate the association between cannabis problems and functional impairment attributed to depression, rather than diagnostic outcomes or symptom severity, which are the constructs seen in most prior research on this relationship. In addition, this study benefits from a number of other strengths. First, the samples used for this

research were drawn by sampling non-institutional dwelling units, and thus, the findings are more likely to generalize to the source population and have increased external validity. Second, the use of factor analysis and structural equation modeling in this research represent steps forward beyond what typically has been used in prior studies on the topic of cannabis and depression. These methods benefit from increased validity and reduced measurement error by operationalizing constructs to be inferred from multiple observed variables; they allowed the testing multiple relationships within a complex model (Anderson & Gerbing, 1988).

Despite these strengths, this study possesses a number of limitations. First, the use of cross-sectional data creates a challenge in ensuring the proper temporal sequence between the suspected exposure and outcomes, which is crucial if the goal is to infer causal relationships (i.e., the chicken-egg problem is unresolved). The time period for the experience of cannabis problems and functional impairment attributed to depression in this study overlapped the same 12 month period prior to interview. The study approach partially addressed this issue via exclusion of exposed cases whose first depression spell preceded or was concurrent with the onset of cannabis smoking. While no differences in the results were found, the possibility that depression-related impairment influences problematic cannabis use, or the possibility of feedback mechanisms, cannot be fully ruled out in these data. Second, this study used the brief measure of functional impairment, the Sheehan Disability Scale (SDS), which contained only five indicators covering four life domains. Alternative measures with a larger number of items and covering more life domains might produce a better measure overall functional impairment, and potentially affect results. A review by McKnight and Kashdan (2009) listed over 20 different measures of impairment used in depression research, including at least three measures that have been used more frequently than the SDS: the Short Form Health Survey (SF-36), the Dyadic Adjustment

Scale (DAS), and the Inventory of Interpersonal Problems (IIP) (Horowitz, Rosenberg, Baer, Ureño, & Villaseñor, 1988; Spanier, 1976; Ware & Sherbourne, 1992). Nevertheless, the psychometric properties of the SDS (i.e., internal consistency and reliability) compare favorably to these other measures (McKnight & Kashdan, 2009). Third, the latent dimension of cannabis problems was only measured in relation to past year experience. Therefore, those with a past history of cannabis problems, but had quit more than a year prior to interview were treated equally on the latent trait of cannabis problems as those who never used cannabis. This might obscure important variation on the potential long-term effects of cannabis problems on later impairment, and potentially underestimate the overall association. Furthermore, the data lacked information on cannabis withdrawal, which has since been included under the DSM-V and was a part of the ICD-10 diagnostic criteria for cannabis use disorders (American Psychiatric Association, 2013; World Health Organization, 1993). Cannabis withdrawal has been associated with both decreased mood and increased impairment (Allsop et al., 2012; Budney & Hughes, 2006; Hasin et al., 2008).

### 5.3. Study 3: Cannabis Problems and History of Blunt Smoking

The aim of this study was to estimate the degree to which a history of cannabis blunt smoking might account for problematic cannabis use experienced in a large, representative sample of cannabis users. Findings suggest that higher levels of cannabis problems are associated with a more recent blunt smoking occurrence and with more frequent days of blunt smoking in the past month when compared to their non-blunt cannabis-using peers. This result persisted in statistical models accounting for differences in sex, age, race/ethnicity, population density, alcohol problems, and tobacco dependence.

Findings such as these are concordant with that of Timberlake (2009), who observed a two-fold excess odds of experiencing a cannabis use disorder for those who primarily smoked blunts. Another study found frequency of blunt smoking to be uniquely associated with more cannabis problems, craving, and negative affect (Ream et al., 2008). These results would appear to contrast qualitative observations of blunt smokers, their rituals, and group consumption norms, which indicated blunt smoking promoted moderation, rather than excessive consumption (Dunlap et al., 2006). Further, an experimental study did report that smoking joints produced higher levels of plasma THC and ratings of intoxication than smoking blunts (Cooper & Haney, 2009). However, the authors disclosed a possible methodological reason for the differences: participants (who were blindfolded) smoked blunts through a cigarette holder, which may have made inhaling smoke through cigar paper more difficult compared to the cigarette paper used for joints.

This study's finding may also be relevant to the prior literature on the co-use of tobacco and cannabis. Much of this work has been done on the lifetime co-use or concurrent use (i.e., both drug compounds used during the same overlapping time periods). These studies have generally found tobacco and cannabis co-use to be associated an increased risk for cannabis use disorders, although there have been a few null findings (Agrawal & Lynskey, 2009; Agrawal et al., 2009; Coffey, Carlin, Lynskey, Li, & Patton, 2003; Degenhardt & Hall, 2001; Patton, Coffey, Carlin, Sawyer, & Wakefield, 2006; Swift, Coffey, Carlin, Degenhardt, & Patton, 2008). Studies that have looked at simultaneous use (i.e., used together or on the same occasion) include one by Ream and colleagues (2008), which found that those who often 'chased' cannabis with tobacco (i.e., smoked tobacco soon after cannabis) were 25%-50% more likely to experience cannabis problems. Work by Agrawal and others (2009) also found women who simultaneously used

tobacco and cannabis were more likely to be a daily cannabis user, to have used cannabis more than 40 times, and to have been diagnosed with DSM-IV cannabis abuse, but not with dependence. However, the degree to which blunt smoking can be generalized in this manner remains unclear. There has been no systematic study of the nicotine content of blunts after much of the tobacco has been removed from the cigar. Therefore, the amount of exposure may be low.

Before a more detailed discussion of the study's findings, it is worth noting some of the more central limitations. Of central concern, with these cross-sectional data, issues of temporal sequencing between blunt smoking and cannabis problems cannot be determined with certainty (i.e., the previously mentioned chicken-egg problem of which came first). Thus, it is possible that problematic cannabis use could have contributed to the incidence or frequency of blunt use. Another potential limitation is the degree to which these findings can be generalized to other populations outside the United States. Blunt smoking appears to be a uniquely American phenomenon, against a background of USA cannabis smoking in which the typical practice is to not mix cannabis and tobacco. This USA situation is in contrast with how people in most other countries consume cannabis (i.e., together with tobacco products), and one might expect these differences would translate into greater risk of cannabis use disorders in these countries. However, this appears to not be the case; greater risk is not always seen elsewhere outside the USA (Perkonigg et al., 1999).

These limitations should be viewed in light of several strengths. First, this study is perhaps the largest investigation of blunt smoking practices among cannabis users, and as such the estimates produced benefited from greater precision and external validity to the U.S. population. Second, blunt smoking appears to be gaining popularity over time as evidenced by this study and previously by Timberlake (2013). Thus, there is an advantage to using data

collected very recently to describe current relationships. Further, given the annual replication of the NSDUH, it is possible to not only quickly and easily replicate these results, but also to characterize population changes over time. Third, the coordinated sampling designs and standardized, computer-assisted survey methods aided in reducing between survey variability and promoting honest, accurate reporting on drug use behaviors and other sensitive topics. Finally, it should be mentioned that this research applied more advanced statistical analysis methods to the measurement and study of cannabis problems (methods not often seen in prior research on cannabis problems). Dimensional approaches to the study of cannabis problems provide a complementary approach to the typical diagnostic or categorical approach.

### 5.4. Study 4: Time to Cannabis Onset and Cannabis Problems

In this cross-national investigation of cannabis-only users, the aim was to study the degree to which the risk of becoming cannabis dependent could be predicted by how quickly (or slowly) individuals transitioned from having a chance to try drugs to eventual cannabis onset. These findings appear to support the hypothesis that those who delay cannabis onset are less likely to be dependent later on and experience less cannabis problems. My results show that, on average, each year increase in delaying cannabis onset after the first opportunity might reduce the risk of cannabis dependence by 20%. An inverse relationship was similarly observed for cannabis problems measured as a continuous latent trait, suggesting a possibly protective effect of TCO across the range of problematic cannabis use experience. These results could not be accounted for by differences in background characteristics (i.e., sex, age, education, income, marital status, and country), age of first internationally regulated drug (IRD) opportunity, current

cigarette smoking status, level of alcohol problems, parent's education, and lifetime history of major depressive episode (MDE).

These findings extend the prior work on identifying who are the most vulnerable to progressing sooner from drug opportunity to use, or from first use to dependence (Chilcoat & Anthony, 1996; Wagner & Anthony, 2002a, 2002b, 2007). Initiating drug or alcohol use later in life has been consistently shown to be associated with a lower risk of experiencing disordered use (Anthony & Petronis, 1995; Behrendt, Wittchen, Höfler, Lieb, & Beesdo, 2009; Breslau, Kilbey, & Andreski, 1993; C. Y. Chen, Storr, & Anthony, 2009; Grant & Dawson, 1997; Lynskey et al., 2003). However, this may be the first study to show that delaying cannabis onset in general, subsequent to the timing of their first chance to use the drug, signals reduced risk of later cannabis problems. One prior study did report an 8% decrease in the odds of drug abuse for each year increase in the time from age of first IRD opportunity to use, controlling for age of first IRD use, type of drug used, and other background factors (Swendsen et al., 2008). A general adverse effect of rapid drug stage transition was observed in a study of cigarette smokers, where quickly progressing from less than weekly to weekly smoking signaled an risk of becoming a daily smoker, and quickly progressing from weekly to daily smoking predicted nicotine dependence (Dierker et al., 2008).

Several mechanisms, individually or in conjunction, might help explain these findings. First, time to cannabis onset could serve as a proxy measure for impulsiveness or risk-taking/sensation-seeking personality traits, which have been shown to be associated with drug use and disorders (Clark, Roiser, Robbins, & Sahakian, 2009; Hoyle, Stephenson, Palmgreen, Lorch, & Donohew, 2002; M. W. Johnson et al., 2010; C. A. Martin et al., 2002; Simons & Carey, 2002; Whitlow et al., 2004). This subgroup may be more likely to use drugs given the

chance, and/or seek out an opportunity to do so. Drug use in turn might affect impulsivity, initiating possible feedback loops and increasing the risk for disordered drug use (Jentsch & Taylor, 1999; McDonald et al., 2003). Second, time to cannabis onset might be a function of the number of cannabis opportunities, which could be affected by environmental and social factors. For example, living in disadvantaged neighborhoods is associated with higher rates of drug opportunity and use conditional on opportunity (Crum et al., 1996; Storr, Arria, Workman, & Anthony, 2004; Storr, Chen, et al., 2004). Parental and peer drug use also appears to have effects on drug use, although debate on this topic continues (J. S. Brook et al., 1998; Buckner, Crosby, Silgado, Wonderlich, & Schmidt, 2012; Chabrol, Mabila, Chauchard, Mantoulan, & Rousseau, 2008; Fergusson & Horwood, 1997; Kandel, 1996; Kuntsche & Jordan, 2006).

The observations from this study should be viewed within the light of several important limitations. When cross-sectional data is used, there is always the concern with selection biases, in which the most seriously involved cannabis users are left out of the sampling frame. In this regard, most WMH surveys did not target youths under age 18 years, population members who lacked a permanent household (e.g., homeless shelters and institutionalized group quarters), those experiencing premature mortality due to cannabis smoking, and rural populations in some surveys (i.e., Colombia, Mexico, Japan, Brazil, and China sampled major metropolitan areas). This research also relied on retrospective self-report data, which is subject to recall bias. While lifetime indicators of drugs use have good reliability, the degree to which respondents could accurately recall the age of their first IRD opportunity and/or cannabis use may be of some concern.

With respect to the size of the sample, many WMH countries lacked sufficient numbers of cannabis-only users and/or cases of cannabis dependence to produce country-specific estimates.

With respect to the measurement of time to cannabis onset, these estimates would have been more informative from a specific measure of the age of first cannabis opportunity, rather than of IRDs in general. However, cannabis tends to be used earlier than other IRDs, and one might reasonably conclude that it is likely the first IRD persons are given a chance to try. Further, the time to cannabis onset variable was measured relatively coarse-grained, and thus it was not possible to probe into potential variation in the risk of later cannabis problems for those who might have quickly transitioned from first opportunity to cannabis use in a matter of days, weeks, or months, which might be more informative.

# CHAPTER 6. CONCLUSIONS

## 6.1. Cannabis Problems and Functional Impairment Attributed to Depression

The results of this study may have important implications as we seek to account for the role cannabis smoking might play in exogenous modulation of the natural history of depression. This research highlights the need and opportunities for investigating alternative clinical endpoints for depression that have been largely overlooked with respect to cannabis smoking. Studies that focus exclusively on identifying risk factors for incidence of depression tend to neglect important issues of severity, duration, recurrence, and impairment that contribute to the overall burden of depression. Given that the totality of evidence suggests cannabis smoking to be at best a very modest correlate or predictor of incident depression, now may be time for researchers focus on alternative explanations to account for co-morbidity findings. Should these findings be replicated, it may signal that individuals with co-occurring depression and cannabis use are particularly vulnerable to more debilitating decrements in the home, work, and interpersonal relationship domains that in turn might exacerbate their depression, and thus be in more need of effective treatment. Likewise, clinicians might be concerned that depressed patients experiencing significant impairment, and who might be also using cannabis, may additionally be in need of treatment for their cannabis smoking. This is illustrated by a study by Green and colleagues (2011), who found that parents were more likely to be aware of their child's drug or alcohol problem if the youth exhibited signs of a high level of functional impairment. General measures of functional impairment (without asking the person to attribute their impairment to any specific cause) might serve as a sensitive indicator for an underlying psychiatric problem the patient may be hesitant to disclose directly, especially if the problem involves illegal drug use.

In summary, individuals with depression and co-occurring cannabis problems experience more functional impairment attributed to their depressed mood. This finding could be the result of cannabis smoking contributing to more severe depression. Well-designed prospective studies would be better equipped to demonstrate the causal sequence and development of these two experiences over time, although there is reason to suspect cannabis smoking having an adverse influence on depression, rather than the reverse. Future studies will need to determine whether cannabis smoking worsens impairment in depression, or if impairment related to cannabis problems is additive, and perhaps misattributed to depression. Perhaps the best evidence might come from randomized experimental treatment trials, where treatment for either depression or cannabis problems might disclose whether there is a corresponding improvement in the other.

### 6.2. Cannabis Problems and History of Blunt Smoking

This research highlights the need for researchers, clinicians, and public health officials interested in the prevention and treatment of cannabis problems to pay particular attention to the phenomena of blunt smoking. This study provides novel evidence that blunt smoking may be a more potent indicator of problematic cannabis smoking as compared to alternative predictors or covariates such as being male or younger. It may be time to reject notions that all forms of cannabis use have similar etiology, use patterns, and consequences, and begin to focus on cannabis subgroups with important distinctions. Qualitative research on blunt smokers has detailed distinctions in the rituals, normative behavior, motivations for use, social identity, symbols, language, and group settings that set them apart from previous generations of cannabis users (Dunlap et al., 2006, 2005; B. D. Johnson et al., 2006; Kelly, 2005; Schensul et al., 2000; Sifaneck et al., 2005; Soller & Lee, 2010). These factors may have important implications for

who among this newer generation start to use cannabis, persist in use, and are at risk for harmful or problematic use.

Blunt smoking may be indicative of cannabis users who are especially in need of treatment services. If so, there might be implications for how prevention/treatment messages are targeted to minority groups. Screening and measurement of individuals in need of treatment could be problematic if blunt smokers experience a different profile of features compared to other cannabis users, as in results shown here. Blunts may be perceived to not be addictive, and if they are perceived as such, the addictive qualities of the preparation might be attributed to the tobacco content, rather than to the cannabis (Dunlap et al., 2006). Some even report the ritual surrounding constructing a blunt to be habit-forming (Dunlap et al., 2006). This may lead some users to disregard the need for treatment after ceasing blunt use, but to continue their cannabis use, possibly concurrently with cigarette smoking. Even within treatment settings, blunt users may have more difficulty quitting given evidence that current tobacco use is associated with poorer treatment outcomes for cannabis use disorders (de Dios, Vaughan, Stanton, & Niaura, 2009; Gray et al., 2011; B. A. Moore & Budney, 2002). Co-treatment for both nicotine and cannabis dependence may be needed. Additionally, interventions could be better targeted to blunt smokers by highlighting the potential risks of both cannabis and tobacco, and focusing messages that appeal to the language, symbols, and culture of blunt smokers.

Public health officials need to be more aware of the role cigars and cigar manufactures play in the marketing, sale, and distribution of products that promote cannabis consumption, which particularly appeal to youths, women, and minorities. These groups are more likely to smoke menthol-flavored cigarettes, which has been shown to affect risk of developing nicotine dependence and abstinence (Dauphinee, Doxey, Schleicher, Fortmann, & Henriksen, 2013;

Reitzel et al., 2013; Rosenbloom, Rees, Reid, Wong, & Kinnunen, 2012; Villanti et al., 2012). Similarly, flavored cigars and 'blunt wraps' may help initiate these groups into cannabis smoking. However, there have been no quantitative studies on the degree to which blunts are the first form of cannabis used. Nevertheless, tighter regulation of the sale of cigars used for blunts may indirectly affect cannabis consumption and problematic use.

In conclusion, cannabis users involved with blunt smoking experience more cannabis problems than their peers who abstain from blunts. Prospective, longitudinal data would be best suited to clarify the degree to which prior blunt smoking might be influencing the development of later cannabis problems. However, the author is unaware of any ongoing prospective studies of cannabis use that ask separately about blunt smoking. New longitudinal studies may be required. In order to separate out the role of blunt smoking from non-blunt cannabis use, and it will also be necessary for questionnaires to be more specific in asking about consumption that is strictly cannabis-only versus blunts. For instance, the NSDUH asked about cannabis use during the past month, and then separately about blunt use, but it could not be determined from these responses whether participants considered days of blunt smoking to also be days of cannabis use. This point may be important to identify groups who use blunts as their primary or sole mode of cannabis consumption versus those whose blunt use may be intermittent within their total cannabis use. Finally, the role blunt smoking plays in the promotion and maintenance of cigarettes, cigars, and nicotine dependence (and possible feedback mechanisms) are of interest and require further investigation.

### 6.3. Time to Cannabis Onset and Cannabis Problems

The results of this study may have important implications as we seek to understand the progression from opportunity, to use, to problematic use of cannabis, and how earlier stages of the process might predict transitions to later stages. Elaboration of the mechanisms behind why some drug users progress very quickly from opportunity to use may develop important new insights into reducing the incidence of cannabis smoking. Conversely, investigations into factors that delay, but not necessarily prevent cannabis onset, may reap new knowledge about the development of the cannabis use disorder process.

These findings may also have implications for the design and evaluation of prevention programs. Drug prevention strategies or programs currently designed for a 'one-sized fits all' approach may benefit from targeting individuals at different stages from pre-opportunity to post-opportunity. For example, resources might also be better allocated to those who have only relatively recently been exposed to a chance to try drugs, rather than those who have already shown a resilience. Further, strategies designed to build cognitive, self-esteem, coping, or peer-social skills targeted to the prevention of drug use (e.g., "Just Say No" campaign or D.A.R.E.), might additionally benefit from novel strategies that seek to push potential drug experimentation into later young adult years, where assuming more adult roles and responsibilities could help prevent drug use escalation. Such strategies could be conceived similar to messages that seek to delay adolescent sexual intercourse and/or reinforce safe-sex practices.

Finally, this research program concludes that cannabis users who have longer lag times from the first chance to try drugs to onset of cannabis smoking may be protected from experiencing later cannabis problems. Future work that might build off these findings include the following: 1) Studies that measure time from first cannabis opportunity to use in more fine-

grained intervals of days, weeks, or months, rather than years; 2) Studies could extend these findings to other drugs, including alcohol, cocaine, heroin, extra-medical prescription drug use, ecstasy, etc.; 3) Studies that incorporate the potential influence of prior opportunities and intervals to use of tobacco and alcohol on time to cannabis onset and later problematic outcomes; 4) Studies that search for subgroup variation by sex or nationality; 5) Studies that investigate whether time to cannabis onset also affects time from cannabis use to onset of the first cannabis problem or disordered use syndrome.

# APPENDIX

**Table A.1.** Spearman rank order correlation matrix between model covariates.

| Model Covariate | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 Cannabis Onset | 1.0 | | | | | | | | | | | | | | | | |
| 2 Years of Cannabis Involvement | 0.9 | 1.0 | | | | | | | | | | | | | | | |
| 3 Cigarette Onset | 0.3 | 0.3 | 1.0 | | | | | | | | | | | | | | |
| 4 Alcohol Onset | 0.0 | -0.1 | 0.2 | 1.0 | | | | | | | | | | | | | |
| 5 Sex | -0.1 | -0.1 | -0.1 | 0.0 | 1.0 | | | | | | | | | | | | |
| 6 Age | 0.0 | -0.1 | 0.1 | 0.1 | 0.0 | 1.0 | | | | | | | | | | | |
| 7 Race/Ethnicity | -0.1 | -0.1 | -0.1 | 0.0 | 0.0 | -0.1 | 1.0 | | | | | | | | | | |
| 8 Survey Year | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 1.0 | | | | | | | | | |
| 9 Education | 0.1 | 0.0 | 0.0 | 0.1 | 0.1 | 0.1 | -0.2 | 0.0 | 1.0 | | | | | | | | |
| 10 Employment | -0.1 | -0.1 | -0.1 | -0.1 | 0.2 | 0.0 | 0.0 | 0.0 | -0.2 | 1.0 | | | | | | | |
| 11 Marital Status | 0.1 | 0.1 | 0.0 | -0.1 | -0.1 | -0.6 | 0.1 | 0.0 | -0.1 | 0.1 | 1.0 | | | | | | |
| 12 # of Times Married | 0.1 | 0.1 | 0.0 | -0.1 | -0.1 | -0.6 | 0.1 | 0.0 | -0.1 | 0.1 | 0.9 | 1.0 | | | | | |
| 13 Family Income | 0.0 | 0.0 | 0.0 | 0.0 | -0.1 | 0.2 | -0.2 | 0.0 | 0.3 | -0.3 | -0.3 | -0.2 | 1.0 | | | | |
| 14 Arrested (Lifetime) | 0.2 | 0.3 | 0.1 | 0.0 | -0.2 | 0.0 | 0.0 | 0.0 | -0.1 | 0.0 | 0.1 | 0.1 | -0.1 | 1.0 | | | |
| 15 Other Illegal Drug Use (Lifetime) | 0.4 | 0.6 | 0.2 | -0.1 | -0.1 | -0.1 | -0.1 | 0.0 | 0.0 | -0.1 | 0.1 | 0.1 | 0.0 | 0.3 | 1.0 | | |
| 16 Population Density | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | -0.2 | 0.0 | -0.1 | 0.0 | -0.1 | -0.1 | -0.1 | 0.0 | 0.0 | 1.0 | |
| 17 Anxiety Disorder (Lifetime) | -0.1 | -0.1 | -0.1 | 0.0 | -0.1 | -0.2 | 0.1 | 0.0 | 0.0 | -0.1 | 0.1 | 0.1 | 0.0 | 0.0 | -0.1 | 0.0 | 1.0 |

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