Abstract

**Objective:** The objectives of this study are to: 1) determine the association between cannabis use and depressive symptoms; 2) quantify the association between cannabis use and intake of antidepressant medications; 3) look at the temporal trend of depressive symptoms and cannabis use in NHANES 2005-2012; and 4) determine the association between cannabis use and cardiovascular diseases.

**Design:** Cross-sectional study.

**Data source:** National Health and Nutrition Examination Survey (NHANES 2005–2012) which is conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention.

**Study population:** Participants of the NHANES (2005–2012) between 18-69 years of both genders. The total analytic sample was 20,150 adults.

**Outcome:** Depression (Patient Depression Questionnaire Score, PHQ9, ≥ 10 versus PHQ-9 score < 10)

**Methods:** We applied NHANES weights to account for complex survey design. To deal with missing observations, we imputed the data using multivariate imputed chained equation. Logistic regression models were generated to get the adjusted odds ratios of the association between cannabis use and depressive symptoms, intake of antidepressant medications, and cardiovascular diseases. We also calculated the weighted prevalence of cannabis use and depressive symptoms.
**Results:** The odds of depressive symptoms are 1.8 (95% CI = 1.36 - 2.34) and 1.05 (95% CI = 0.06 - 1.36) among regular cannabis female and male users, compared to non-users or non-regular users, respectively. The odds of depressive symptoms (in both genders) among those who smoked two to five joints and six or more joints per day are 1.23 (95% CI = 1.07 - 4.2) and 2.21 (95% CI = 1.07 - 4.2), respectively, compared to those who use one joint per day. Quitting cannabis for more than a month is associated with less odds of depressive symptoms. The odds of depressive symptoms decreased by 54% (95% CI = 0.27 - 0.82) and 32% (95% CI = 0.31 - 1.07), among women and men respectively, for those who quit cannabis for ≥ one month compared to those who quit for less than one month. The logistic model shows that there was no significant association between cannabis use and intake of antidepressants. The odds of regular cannabis use is 0.81 among women receiving antidepressants, compared to those not receiving antidepressants (95% CI = 0.21 - 3.1). The odds of regular cannabis use is 1.87 among men receiving antidepressants, compared to those not receiving antidepressants (95% CI = 0.44 - 7.9). The prevalence of depressive symptoms among women is 6.7%, 10.1%, 9.7%, and 9.4% in NHANES cycles 2005-2006, 2007-2008, 2009-2010, and 2011-2012, respectively. The prevalence of depressive symptoms among men is 5.1%, 7.1%, 7%, and 6.8% in cycles 2005-2006, 2007-2008, 2009-2010, and 2011-2012, respectively. The prevalence of regular cannabis use among women is 17% 15.5% 19.9% 20.7%, in cycles 2005-2006, 2007-2008, 2009-2010, and 2011-2012, respectively. The prevalence of regular cannabis use among men is 24.2%, 23.3%, 27.1%, 27.5% in cycles 2005-2006, 2007-2008, 2009-2010, and 2011-2012, respectively. We did not find a significant association between
cannabis use (even heavy use) and cardiovascular diseases (OR=1.07 & 95% CI=0.82-1.40)

**Conclusions:** Cannabis use is associated with higher depressive symptoms, particularly among women. Quitting cannabis for more than a month is associated with lower depressive symptoms, particularly among women. We did not find an association between cannabis use and intake of antidepressants which suggests that depression treatment might help to decrease use of cannabis. Cannabis use prevalence dropped in 2007-2008 cycle then rose again in the following cycles, which is an alarming finding. The prevalence of depressive symptoms increased in 2007-2008 cycles then dropped slightly in the following cycles. Our analysis did not reveal an association between cannabis use and cardiovascular diseases.
Dedication

This document is dedicated to the soul of my mother, my father, and my family.
Acknowledgments

I would like to express my appreciation to the people who have played a valuable role in completion of my graduate studies.

First and foremost, I would like to thank my advisor Dr. Randall Harris, whose constant support and guidance helped me during my study at the Ohio State University. The knowledge that I have gained from him while working on this dissertation and throughout my graduate career has been truly appreciated and will not be forgotten. I hope that we will continue to collaborate on future research endeavors throughout my academic career.

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I am grateful to my colleagues and staff members in the department of Epidemiology, College of Public Health at the Ohio State University.

My sincerest gratitude goes out to my mother, my father, my sisters and my children. They have been a constant source of support, wisdom and inspiration. Their effort and sacrifice throughout my entire education are very much appreciated.
If there is anyone else who did not receive an acknowledgement, please know that it was not intentional. I have valued you in my life during this undertaking and have appreciated everything that you have done for me.
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Fields of Study

Major Field: Public Health
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Chapter 1: Introduction

1.1 Cannabis epidemiology and pharmacology

Cannabis, also known as marijuana, is the most commonly used illegal substance worldwide. It has been estimated that approximately 160 million people (4% of the world’s population) between the ages of 15 and 64 have used cannabis. The prevalence of marijuana use was on the rise in the 1990s, with a simultaneous decline in the perception that marijuana use is harmful (Leggett 2006). The World Health Organization (WHO) Mental Health surveys were conducted in 17 countries between 2001 and 2005 to determine the prevalence of cannabis use. The surveys sampled individuals 16 years and older and showed that the United States has the highest prevalence, and 51.6% of the population (16-34 years) reported a previous use of cannabis. On the other hand, China has the lowest prevalence of cannabis use, reaching about 3% (Degenhardt, et al. 2008).

Both lifetime and annual cannabis use are significantly higher in younger compared to older people, and in men compared to women. The World Drug Report 2011 showed that the annual prevalence of cannabis use in the United States is 13.7%. The annual prevalence of cannabis use is significantly greater for blacks (10.6%) than whites (8.9%) or Hispanics (8.6%) and is significantly less for college graduates compared to those who did not graduate high school. There were no significant differences in the rate of cannabis dependence between those residing in urban areas and those in rural areas.
Family income was also not found to be significantly associated with cannabis dependence (Kandel, et al. 1997). Due to changing cultivation methods and genetic modifications, the potency of cannabis has been steadily increasing which indicate that users are more likely to consume excessive doses. The average concentration of the active ingredients was 3.4% in 1993 and increased to about 8.8% and 13% in 2008 and 2014, respectively (Cascini, et al. 2012). Being a highly dynamic substance, constant reassessment of the effect of cannabis on physical and mental health is important. This is particularly more relevant in the United States, given the potential for increased medical marijuana use.

Cannabinoid receptors (Figure 1) are present throughout the body and are embedded in cell membranes. Two subtypes of cannabinoid receptors (CB1 and CB2) have been identified. CB1 receptors are predominantly present in the central nervous system, lungs, liver, and kidney. CB2 receptors are predominantly found in immune cells (Pacher and Mechoulam 2011). CB2 receptors have been found to be upregulated by pro-inflammatory cytokines in endothelial cells (Rajesh, et al. 2007).

In the human brain, the cannabinoid receptor type 1 (CB1) binding sites are localized mainly associated with higher cognitive functions (forebrain region) control of movement (midbrain and hindbrain regions). The CB1 binding sites were also found in the limbic system, the center of the brain controlling emotions (Glass, et al. 1997). The cannabinoid receptors CB1 have been found to be activated by anandamide, an endocannabinoid generated naturally inside the body (Mechoulam, et al. 1995) or introduced into the body as cannabis or a related synthetic compound. Pharmacological
inhibition of the anandamide degrading enzyme, fatty acid amide hydrolase, augments anandamide-mediated cannabinoid receptor signaling and has been shown to reduce unconditioned anxiety and despair behaviors in animal models (Gunduz-Cinar, et al. 2013b). Stress exposure has been shown to decrease anandamide levels in several limbic brain regions. This suggests that the decrease in anandamide signaling contributes to the stress-induced anxiety-like behavior (Gunduz-Cinar, et al. 2013a). This observation may explain how cannabis use may alleviate the symptoms of anxiety and depression.

![Distribution of cannabinoid receptors](image)

**Figure 1: Distribution of cannabinoid receptors**

1.2 **Cannabis and psychological domains**

Evidence of an association between cannabis use and long-term neurocognitive deficits is not yet very consistent. A meta-analysis conducted in 2003, included more than 600 cannabis users, has found no association between cannabis smoking and significant
long term effects on neurocognitive processes (Grant, et al. 2003). On the other hand, Lyons and colleagues have studied cognitive parameters such as general intelligence, attention, memory executive functioning, and motor skills on marijuana-using twins and their non-using co-twins. Among these parameters, only general intelligence was significantly different between marijuana users and non-marijuana user twin pairs (Lyons, et al. 2004). A prospective study in New Zealand, following 1,037 individuals from birth to age 38 years, also has found an association between persistent cannabis use and neuropsychological decline. In that cohort, adolescent-onset cannabis users had a greater cognitive decline (Meier, et al. 2012).

A systematic review of 35 longitudinal studies has found a 41% increased risk of psychosis for those who ever used cannabis compared to respective controls (95% CI 1.20-1.65) (Moore, et al. 2007). The study has suggested of the dopamine release as a mechanism of cannabis-induced psychosis. As an attempt of explaining the higher risk of psychosis among cannabis users, a study has shown a functional polymorphism in the catechol-O-methyltransferase (COMT) gene in those cannabis users at high risk of psychosis (Caspi, et al. 2005).

There is substantial evidence that the nucleus accumbens and amygdala (subcortical areas of the limbic brain system regions responsible for the processing and storage of short term memory, reward circuits, and moods), play an important role in the pathophysiology of depression (Shirayama and Chaki 2006). Serotonin and dopamine receptors are found throughout the limbic system which is involved in forming
associations between emotional stimuli and environmental cues (Pockros-Burgess, et al. 2014). Studies have reported that deep brain stimulation of the nucleus accumbens was successful in decreasing depression symptoms (Bewernick, et al. 2010). Major depressive disorder has also been associated with volumetric abnormality in the amygdala (Hamilton, et al. 2008). A neuroimaging study has found a significant association between the long term heavy use of cannabis and a morphological disruption in the left nucleus accumbens and right amygdala (Lorenzetti, et al. 2015). This finding is consistent with animal (Kolb, et al. 2006) studies that suggested marijuana exposure is associated with structural alterations of these important brain regions.

A cross-sectional survey, 277 same-sex twin pairs discordant for cannabis dependence and 311 pairs discordant for early-onset cannabis use (before age 17 years), has found that early major depressive disorder and suicidal ideation were significantly associated with use of cannabis, at an early age, in discordant dizygotic pairs but not in discordant monozygotic pairs (Lynskey, et al. 2004).

A recent meta-analysis of 14 longitudinal studies examining the association between cannabis use and depression has found that cannabis is associated with a modest increased risk for developing depressive disorders. Odds ratio= 1.17 (95% CI=1.05–1.30). Heavy cannabis use was associated with a stronger risk. Odds ratio= 1.62 (95% CI 1.21–2.16) (Lev-Ran, et al. 2014). However, most of the individual studies selected for the meta-analysis had a small sample size which made it difficult to control for possible confounding variables.
Furthermore, it has been suggested that marijuana has been a coping strategy for stress and anxiety. Buckner and colleagues have found that college students often use cannabis to cope with their social anxiety (Buckner, et al. 2012). Using marijuana to cope with negative emotions may make it harder for users to quit the drug. It has been found that people who self-medicate by using marijuana to alleviate anxiety are seven times more likely to become addicted to marijuana (Buckner, et al. 2007; Buckner and Schmidt 2009; Buckner, et al. 2008; Buckner and Turner 2009).

Conclusively, the relationship between poor depressive symptoms and cannabis use seems to be a vicious circle that has to be broken. To treat cannabis use disorders, it may be beneficial to find alternative mood-regulation strategies to replace marijuana.

1.3 Depression epidemiology and etiology

Depression is a mental illness that can be debilitating and costly to patients and their families. Depression can also adversely affect the course and outcome of chronic medical conditions, such as cardiovascular diseases, cancer, diabetes, and obesity. On the public health level, depression is a leading cause of increased work absenteeism, disability, and decreased productivity. The annual economic consequences of depression were estimated to be 83 billion dollars in the United States in 2000 (Donohue and Pincus 2007).

The prevalence of depression is on the rise. A study comparing 1991 to 1992 data with 2001 to 2002 data collected from two nationally representative surveys of the United States (N >40,000 per sample) has found that the prevalence of depression is escalating
over time. The point prevalence of major depression more than doubled in this time period (3 to 7%) (Compton, et al. 2006). In 2012, the National Institution of Health (NIH) has estimated that 16 million adults (6.9 % of the US adults) 18 year or older in the U.S. had at least one major depressive episode in 2011.

The prevalence of depression has been found greater in females compared to males. In the United States, a nationally representative study of adults in 2005 has found that the 12 month prevalence of major depression in females and males was 7 and 4 %, respectively (Hasin, et al. 2005). A survey conducted in 2007 on American adults has reported the lifetime prevalence of major depression of 18, 13, and 10 % for Whites, Caribbean Blacks, and African Americans, respectively (Williams, et al. 2007). However, major depression was more prolonged and associated with functional impairment in both African Americans and Caribbean Blacks, compared with Whites.

Major depression is more common in younger than older adults. A survey conducted on more than 9,000 US adults in 2010 has found that the lifetime prevalence of major depression in those 65 years and older was significantly less (10%), compared with younger age groups (19-23 %) (Kessler, et al. 2010). A survey of approximately 2,600 United States adults aged 55 years and older has found that the twelve-month prevalence of major depression declined significantly with increasing age (Byers, et al. 2010). Therefore, the productivity of the younger population might be more impacted by depression.

According to the WHO report of 2010, major depression carries the heaviest burden of disability among mental and behavioral disorders as it causes 8.3 % of all U.S
populations to live with disability. Each year lived with depression has been calculated to
detract approximately 20% to 40% from a quality adjusted life year (Fryback, et al.
1993).

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-
5), published on May 2013, has identified major depressive syndrome with five or more
of the following symptoms: depressed mood, loss of interest or pleasure in most or all
activities, insomnia or hypersomnia, change in appetite or weight, psychomotor
retardation or agitation, low energy, poor concentration, thoughts of worthlessness or
guilt, and recurrent thoughts about death or suicide. At least one of the symptoms, either
depressed mood or loss of interest or pleasure, should be present most of the day nearly
every day for a minimum of two consecutive weeks in combination with another four
symptoms (Roehr 2013). Depression can be mild to moderate with symptoms of apathy,
little appetite, difficulty sleeping, low self-esteem, and low-grade fatigue. Minor
depressive disorder does not meet full criteria for major depression but at least two
depressive symptoms are present for two weeks. It is given in the DSM-5 as an example
of a depressive disorder not otherwise specified (Rapaport, et al. 2002).

Depression is an etiologically complex disorder that has a multiple interrelated
risk factors acting at different stages of development. These multiple, interacting factors
constitute three broad pathways for developing the illness; internal, external, and
psychosocial factors. Internal factors include genetics, low self-esteem, and neuroticism
(a personality trait defined by anxiety, fear, moodiness, worry, envy, frustration, jealousy,
and loneliness). External factors include substance misuse, and conduct disorder which is
a psychological disorder diagnosed in childhood or adolescence that presents with persistent pattern of behavior in which the basic rights of others are violated. Psychosocial factors include trauma during childhood or adulthood, stressful life events in past year, parental loss, low parental warmth, history of divorce, marital problems, low social support, or low education (Kendler, et al. 2006).

Depression involves abnormal functioning of many neurotransmitters. The role of the serotonergic system in depression has been established. Acute tryptophan (the precursor amino acid required for central synthesis of serotonin) depletion in patients with major depression, treated with selective serotonin reuptake inhibitors, often causes a severe, rapid relapse (Booij, et al. 2005). Norepinephrine and dopamine neurotransmitters are known to help with depression and focus. A study has found that patients with major depression treated with desipramine, a norepinephrine reuptake inhibitor, had a relapse after taking alpha-methyl-para-tyrosine (which rapidly depletes catecholamines by inhibiting their synthesis) but not after taking placebo (Klein, et al. 2011). Cannabis smoking causes temporary rise in dopamine levels leading to the euphoria that smokers experience. However, it has been found that regular long-term cannabis use is associated with a dose-dependent reduction in dopamine synthesis (Bloomfield, et al. 2014).

Numerous studies have implicated changes in GABA and glutamate in the pathophysiology of depression. A magnetic resonance spectroscopy protocol has observed elevated levels of glutamate and lower levels of GABA in the occipital cortex of subjects diagnosed with major depression. It has been shown that stimulation of CB1 receptors resulted in the inhibition of the neurotransmitter GABA which may cause
depression among chronic cannabis users (Sanacora, et al. 1999).

1.4 Cannabis and the cardiovascular system

Preclinical studies have indicated that acute administration of Tetrahydrocannabinol (THC) increases dopamine levels by different mechanisms. THC has shown to increase limbic dopaminergic neuron firing rates via endocannabinoid CB1 receptor stimulation, inhibit striatal dopamine reuptake, selectively increase tyrosine hydroxylase expression, and increase dopamine release and synthesis (Caspi, et al. 2005; Lorenzetti, et al. 2015; Lynskey, et al. 2004; Moore, et al. 2007).

Dopamine is the direct precursor of other catecholamines epinephrine and norepinephrine. Activation of the sympathetic nervous system leads to release of catecholamines and stimulation of the adrenergic receptors, leading to an increase of the heart rate and vasoconstriction. The stimulant action of cannabis on the cardiovascular system, through stimulation of the sympathetic nervous system, has shown to increase the oxygen requirement of the myocardium which may consequentially lead to ischemia. In addition, the vasospasm, related to norepinephrine release, may also contribute to myocardial ischemia (Lev-Ran, et al. 2014). Because of these diverse actions, cannabis use might present with very different cardiovascular system findings.

An epidemiological retrospective study demonstrated that smoking cannabis could trigger acute coronary syndrome, with the first hour after smoking being a high risk for occurrence of myocardial infarction (Grant, et al. 2003). This effect could probably be explained by the positive effect of cannabis on the dopaminergic system.

Cannabinoid receptors CB1 and CB2 have been found in the cardiovascular
system and can be directly affected by THC, independent of the autonomic nervous system. Intravenous administration of cannabinoid receptor agonists had a bradycardic effect and been shown to increase the duration of the QRS complex in rats. This effect was due to stimulation of CB1 receptors in the heart since it was not observed after CB1 receptor blockade. Also this bradycardic action was independent of the autonomic nervous system because it remained significant after blocking the autonomic ganglion (Buckner, et al. 2012).

Previous research has shown an equivocal effect of cannabis on the pathogenesis of atherosclerosis. Inflammation plays an essential role in atherosclerosis and therefore, cannabinoids can affect the atherogenic process via modulation of the immune system (Leggett 2006). Animal studies have shown that low dose of THC (1mg/kg/day), which is much lower than the dose associated with psychological effect, has a protective effect against atherosclerosis development in the aortic root (Degenhardt, et al. 2008). This protective effect could be explained by the lipolysis action of THC and the stimulation of CB2 receptors which may lead to a decrease in the pro-inflammatory cytokine gene expression (Cascini, et al. 2012; Kandel, et al. 1997). On the contrary, it has been suggested that stimulation of CB1 receptors promotes the inflammatory and atherogenic process. Han et al have shown that giving CB1 antagonist, rimonabant, decreased the pro-inflammatory cytokine gene expression in mice (Pacher and Mechoulam 2011). Several clinical trials have shown that cannabis does not have a role in the inflammation and atherogenic process and their clinical outcomes (Begg, et al. 2005; Gunduz-Cinar, et al. 2013a; Gunduz-Cinar, et al. 2013b).
1.5 Depression screening

The Patient Health Questionnaire (PHQ-9) is a self-administered questionnaire version of the PRIME-MD diagnostic instrument for common mental disorders (Kroenke, et al. 2001). The PHQ-9 is the depression module, which scores each of the nine DSM-IV criteria as "0" (not at all) to "3" (nearly every day).

Validity of PHQ-9 has been assessed against an independent structured mental health professional interview. PHQ-9 score ≥10 had a sensitivity of 88% and a specificity of 88% for major depression and it can be used over the telephone (Pinto-Meza, et al. 2005). Therefore, PHQ9 is a reliable and valid measure of depression severity. Correlation between the PHQ-9 completed by the patient in the clinic and that administered over the phone by the Mental Health Professional Interview within 48 hours was 0.84, and the mean scores were nearly identical (5.08 vs 5.03) (Sanacora, et al. 1999). PHQ-9 have been used as a continuous measure of depression severity. PHQ-9 scores of 5-9, 10-14, 15-19, and 20-27 represent valid thresholds demarcating the lower limits of mild, moderate, moderately severe, and severe depression, respectively (Kroenke, et al. 2001).

First-line treatment of depression consists of psychotherapy and somatic therapy (medication or electroconvulsive therapy). The choice of treatment depends upon the severity, type, and chronicity of the depressive episode, contraindications to medication, treatment access, and patients’ preference. Psychotherapy and pharmacotherapy may be used alone or in combination. For moderate to severe forms of depression, pharmacotherapy is recommended (Arean and Cook 2002).
1.6 Objectives

Owing to the escalating prevalence of cannabis use, its incremental increased potency, and the substantial evidence that cannabis and depressive symptoms contribute to a viscous circle, this study is designed to fulfill the following objectives:

1) Compare the use of cannabis among individuals suffering from depression with individuals without depression, within 4 NHANES cycles (2005-2006), (2007-2008), (2009-2010), and (2011-2012), controlling for possible confounding factors (assessed by a Directed Acyclic Graph; DAG) to determine the joint contribution of cannabis use with other variables, particularly those not thoroughly explored in previous studies such as lack of physical exercise, education level, comorbidity, and body mass index.

2) Determine if there is a significant difference in cannabis use among patients with depression receiving antidepressant medications and those not receiving antidepressant treatment within 4 NHANES cycles (2005-2006), (2007-2008), (2009-2010), and (2011-2012).

3) Estimate the period prevalence of cannabis use as well as depression in each of the following NHANES cycles: (2005-2006), (2007-2008), (2009-2010), and (2011-2012). This will help to determine temporal trends in the prevalence of cannabis use and depression from 2005 through 2012.

4) Explore the association between cannabis use and cardiovascular diseases, controlling for possible confounding factors.
Chapter 2: Methods

2.1 Study design and sampling

This is a cross-sectional population-based study derived from the National Health and Nutrition Examination Surveys (NHANES). NHANES is a program of studies designed to assess the health and nutritional status of adults and children in the United States (Hyattsville 2012). NHANES data are collected annually and released in two-year cycles. The survey utilizes stratified, multistage probability sample of non-institutionalized (not inmates of institutions such as penal, mental facilities, homes for the aged), United States civilians. In each cycle, approximately 5000 individuals participate in a detailed home-based interviews, physical examinations that occur at a mobile examination center (MEC), and laboratory investigations. The NHANES interview includes demographic, socioeconomic, dietary, and health-related questionnaire. The examination component consists of medical, dental, and body measurements, as well as laboratory tests. The first NHANES was conducted in 1971 and has become an annual event in 1999 (continuous NHANRS) (Spitzer, et al. 1999). Our study population was drawn from (2005-2006), (2007-2008), (2009-2010), and (2011-2012) NHANES cycles and includes men and women from 18-69 years old. For the purpose of this project, we examined each of the previous cycles individually and then used all cycles combined for the pooled analysis.
2.2 Data collection and management

2.2.1 Depression status

Depression was measured using the PHQ-9, a nine-item screening instrument that asked questions about the frequency of depression symptoms over the past 2 weeks (Arroll, et al. 2010). A final follow-up question assessed the overall impairment of the depressive symptoms. PHQ-9 has a total score of 27 and has been found as a reliable and valid screening tool with acceptable diagnostic properties for detecting major depressive disorder for cut-off scores between 8 and 11 (Arroll, et al. 2010; Zhang, et al. 2013). Response categories for the nine-item instrument were "not at all," "several days," "more than half the days" and "nearly every day".

A cut-off score of 10 showed a sensitivity of 0.89 and a specificity of 0.97, with an area under the curve of 0.977 (95% confidence interval: 0.97-0.99). The internal consistency of PHQ-9 was 0.85 (95% confidence interval [CI]: 0.839–0.867), as established by Cronbach’s α coefficient (Zhang, et al. 2013). For the purpose of the analysis, depression status was categorized into two categories using a cut point score of 10.

The depression screening questions were asked by trained interviewers, using the Computer-Assisted Personal-Interview (CAPI) software that uses private interviews conducted in Spanish or English (Murphy, et al. 2000). No proxies or interpreters were permitted for these questions (Manea, et al. 2012). The CAPI system was programmed with a built-in consistency check tool to reduce data entry errors.
2.2.2 Status of cannabis use

NHANES has collected data on cannabis use through an Audio-Computer-Assisted Self-Interview (ACASI) software questionnaire. In NHANES, cannabis use (self-reported) was measured by asking the following questions: 1) Have you ever used marijuana; 2) How old were you the first time you used marijuana; 3) When did you use marijuana regularly; 4) How long has it been since you used marijuana every month for a year; 5) How often have you used marijuana; 6) How many days have you used marijuana or hashish per month; 7) What was the last time you used marijuana or hashish; 8) How many joints have you smoked every day (assessed only in 2009-2010 and 2011-2012); and 9) How long has it been since you used marijuana (assessed only in 2009-2010 and 2011-2012)

For the purpose of the analysis, new variables were created as shown in table 1.
Table 1: Cannabis use parameters

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
<th>NHANES Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular cannabis use</td>
<td>Regular smoking at least once a month versus non-use or non-regular use</td>
<td>2005 through 2012</td>
</tr>
<tr>
<td>Frequency of use</td>
<td>Eight times or more per month versus less than 8 times a month</td>
<td>2005 through 2012</td>
</tr>
<tr>
<td>Dose of cannabis</td>
<td>Two, three to five, and six and more joints per day versus one joint a day</td>
<td>2009 through 2012</td>
</tr>
<tr>
<td>Quitting cannabis</td>
<td>Quitting for a month or more versus quitting for less than a month</td>
<td>2009 through 2012</td>
</tr>
</tbody>
</table>
2.2.3 Covariates

A directed acyclic graph (DAG) was generated, as a tool to determine what to adjust for in the regression model (Textor, et al. 2011). Based on the DAG shown in figure 2, age, gender, race, education, cigarette smoking, and alcohol were considered to be potential confounder variables. Lack of physical exercise, comorbidity, and obesity were tested in the regression model as direct causes of depression. Comorbid conditions included in this study were congestive heart failure, angina, myocardial infarction, stroke, diabetes, COPD, and malignancy. Interaction terms were also tested in the regression models.

Serum cotinine (a metabolite of nicotine) level was used to detect tobacco smoking status as it is more accurate than self-reported smoking data. A cut-off point of 3 ng/ml of cotinine was used to distinguish smokers from nonsmokers. The rationale for using this cut point is based on the analysis of data from a large, nationally representative group of American smokers and nonsmokers. This analysis has indicated that the optimal overall cut-off point for minimizing the rate of misclassification of self-reported smoking status is a serum cotinine concentration of 3 ng/ml. This cut-off point has an excellent discriminative ability as it has a high degree of sensitivity (87.5) and specificity (93.1), giving it (Benowitz, et al. 2009).
Figure 2: Cannabis and depression association. This Dag shows the confounding variables that are related to both exposure (cannabis) and outcome (depression) in red color. The variables that are directly related to the outcome are shown in black. Lack of physical exercise, education level, comorbidity, and body mass index variables were not thoroughly explored in previous studies.
Table 2: Covariates used for the analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Categorical variable: 18-29 (ref), 30-40, 40-50, &amp; 50-69</td>
</tr>
<tr>
<td>Gender</td>
<td>Binary: females (ref) and males</td>
</tr>
<tr>
<td>Race</td>
<td>Categorical variable: blacks (ref) Hispanics, whites, &amp; Other Race</td>
</tr>
<tr>
<td>Education level</td>
<td>Categorical variable: &lt; high school (ref), high school grad, some college, &amp; college grad or more</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>Binary: serum cotinine level &lt; 3 ng/ml (ref) &amp; serum cotinine level ≥ 3 ng/ml.</td>
</tr>
<tr>
<td>Physical exercise*</td>
<td>Binary: no exercise (ref) &amp; moderate or vigorous exercise</td>
</tr>
<tr>
<td>Obesity level</td>
<td>Binary: BMI&lt; 30 Kg/M² (ref) &amp; BMI ≥ 30 Kg/M²</td>
</tr>
<tr>
<td>Comorbidity**</td>
<td>Binary: No comorbid conditions (ref) &amp; associated comorbid conditions</td>
</tr>
</tbody>
</table>

*The individual was considered to practice moderate or vigorous exercise if he/she answered “yes” to the questions: “do you do a physical work that cause small increase in breathing or hear rate as brisk walking?” and “do you do a physical work that cause large increase in breathing or hear rate as lifting heavy loads?”

** The binary variable comorbidity =1 if the subject reported a history of cardiovascular diseases, stroke, diabetes, COPD, and/or malignancy. The binary variable comorbidity = 0 if the subject does not have any of those chronic conditions.
2.3 Antidepressant medications

The prescription medications subsection of NHANES questionnaire provides personal interview data on the use of prescription medications during a one-month period prior to the survey date. Questions about prescription medications were asked, in home, by trained interviewers using the CAPI software. Participants over 16 years of age answered for themselves without a proxy (Hyattsville 2005-2012).

The National Center for Health Statistics (NCHS) using the Lexicon Plus, a comprehensive database of all prescription and some nonprescription drug products available in the U.S. drug market, to assist with data collection, editing, and release. Antidepressant medications use was coded with “249”. In our analysis, an indicator variable was created to be “1” if the individual has 249 code or “0” if otherwise.

2.4 Cardiovascular conditions

Cardiovascular conditions were self-reported. In our analysis, an indicator variable was created to be “1” if the subject reported a history of congestive heart failure, angina, heart attack, or stroke. An indicator variable “zero” was created for otherwise individuals.

2.5 Power calculation

Based on the estimated cannabis use (13%) among the United States population, the power of our study is calculated to be 80% in each of the NHANES cycles. The power of 80% is sufficient to detect 4% difference between the two proportions (cannabis smoking prevalence with or without depression).
By pooling the four NHANES cycles, the power of the study is calculated to be 90%, which is sufficient to detect 2.5% difference in cannabis use. The following formula was used to calculate the study power: 

\[ n = \left( \frac{Z_{\alpha/2} + Z_{\beta}}{Z_{\alpha/2} + Z_{\beta}} \right)^2 \times \frac{p_1(1-p_1) + p_2(1-p_2)}{(p_1-p_2)^2} \] 

(Friedman, et al. 2010) where \( Z_{\alpha/2} \) is the critical value of the normal distribution at \( \alpha/2 \) (for a confidence level of 95%, \( \alpha \) is 0.05 and the critical value is 1.96), \( Z_{\beta} \) is the critical value of the normal distribution at \( \beta \) (for a power of 80%, \( \beta \) is 0.2 and the critical value is 0.84) and \( p_1 \) (13%) and \( p_2 \) are the expected sample proportions of the two groups (depressed and non-depressed).

2.6 Statistical analysis

Data are publicly available and provided by the National Center for Health Statistics. The demographics, depression screening data, drug use, alcohol use, physical activity, medical conditions, and body measurements data of each NHANES cycle were merged into master files and additional variables were created for our analysis as shown in table 2. The merged files, for each two year cycle, were appended for the pooled analysis.

2.6.1 Imputing missing data

The percentage of missing values across variables ranges from 4% to 47% (as shown in table 3) therefore, the data were imputed by chained equations to deal with missing observations. The principle of imputation has been explained in details by Stuart and colleagues (Stuart, et al. 2009). Briefly, the variable with the least proportion of missing values is imputed using all variables with no missing values. The variable with
the second least proportion of missing values is then imputed using variables with no missing values and the variable that was imputed in the first imputation step, and so on. One cycle of imputation of variables (iteration) produced data with no missing values. Therefore, all the variables in the model are used in the imputation process. According to Stuart and colleagues, 10 iterations are enough to stabilize the imputation such that the order in which variables were imputed no longer matters. The imputed values at the end of the 10th iteration, combined with the observed data, constitute one imputed data set. This entire process is then repeated to create multiple imputed data sets, such that, to create 10 complete data sets. At the end of the process, a total of $10 \times 10$ iterations are performed.

In our study twenty iterations were performed to impute all the variables with missing observations. The data were also analyzed without being imputed to test the difference between both analyses.
### Table 3: Frequency of missing observations (NHANES 2005-2012)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Available Sample</th>
<th>Missing Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular cannabis use</td>
<td>10,526</td>
<td>9624 (47%)</td>
</tr>
<tr>
<td>Alcohol Status</td>
<td>14,327</td>
<td>5823 (28%)</td>
</tr>
<tr>
<td>Depression status</td>
<td>17,475</td>
<td>2675 (13%)</td>
</tr>
<tr>
<td>Cotinine level</td>
<td>18,268</td>
<td>1882 (9%)</td>
</tr>
<tr>
<td>Education level</td>
<td>18,643</td>
<td>1507 (7%)</td>
</tr>
<tr>
<td>Obesity level</td>
<td>19,289</td>
<td>861 (4%)</td>
</tr>
<tr>
<td>Age</td>
<td>20,150</td>
<td>0.00 (0%)</td>
</tr>
<tr>
<td>Gender</td>
<td>20,150</td>
<td>0.00 (0%)</td>
</tr>
<tr>
<td>Race</td>
<td>20,150</td>
<td>0.00 (0%)</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>20,150</td>
<td>0.00 (0%)</td>
</tr>
</tbody>
</table>
2.6.2 Weighting adjustment

Weights are created in NHANES to account for the complex survey design, including oversampling, survey non-response, and post-stratification. A sample weight is assigned to each sample person. It is a measure of the number of people in the population represented by that sample person. When a sample is weighted in NHANES it is representative of the U.S. Census civilian non-institutionalized population. To produce estimates appropriately adjusted for survey non-response, all variables were checked and the weight for the smallest subpopulation (either “interview only” weight or “interview plus medical exam” weight) was used in the analysis (CDC 2013).

In our analysis, we used the medical examination weight as it was found to be the smallest subpopulation. According to the CDC guidelines, for the pooled analysis, weights were rescaled so that the sum of the weights matches the survey target population at the midpoint of that period.

2.6.3 Logistic regression analysis

Logistic regression models for survey data were generated in STATA using the “mi estimate: svy:” command to account for the complex sampling design.

**Model building:** Purposeful selection of variables in logistic regression, with the depression binary variable as the outcome, was used to select the significant variables (Hosmer, et al. 2013). Briefly, univariate models were conducted, one at a time, for cannabis use, age, gender, race, smoking status, alcohol status, education level, obesity, and comorbidity. Variables having a p value >0.2 were excluded. A multivariate model
having all variables with $p \leq 0.2$ was conducted. To build the final main effect model, variables having $p > 0.05$ were excluded from the model using a backward approach. Interaction terms between gender and other variables were created, added one by one to the main model, and the significant ones (having $p < 0.05$) were kept in the final model.
Chapter 3: Results

The analysis conducted for each individual cycle of the four INHANES cycles studied yielded similar results; therefore, we have reported the pooled analysis for the four cycles.

3.1 Cannabis-depression association

Table 4 shows the weighted demographic and clinical characteristics stratified by gender for individuals 18-69 year-old.
Table 4: Weighted demographic and clinical characteristics of study participants stratified by gender (18-69 years) and drawn from NHANES 2005 to 2012 (unweighted n=20,150)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Men (unweighted N=9,857)</th>
<th>Women (unweighted N=10,293)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>95 % CI</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-29</td>
<td>0.25</td>
<td>0.24-0.27</td>
</tr>
<tr>
<td>30-39</td>
<td>0.20</td>
<td>0.19-0.21</td>
</tr>
<tr>
<td>40-49</td>
<td>0.22</td>
<td>0.21-0.23</td>
</tr>
<tr>
<td>50-69</td>
<td>0.33</td>
<td>0.31-0.35</td>
</tr>
<tr>
<td><strong>Race/ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blacks</td>
<td>0.11</td>
<td>0.10-0.13</td>
</tr>
<tr>
<td>Hispanics</td>
<td>0.16</td>
<td>0.13-0.18</td>
</tr>
<tr>
<td>Whites</td>
<td>0.66</td>
<td>0.62-0.69</td>
</tr>
<tr>
<td>Others</td>
<td>0.07</td>
<td>0.056-0.077</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>0.19</td>
<td>0.18-0.21</td>
</tr>
<tr>
<td>High school grad</td>
<td>0.24</td>
<td>0.23-0.26</td>
</tr>
<tr>
<td>Some college</td>
<td>0.29</td>
<td>0.28-0.30</td>
</tr>
<tr>
<td>College grad +</td>
<td>0.28</td>
<td>0.25-0.30</td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cotinine&lt;3ng/ml</td>
<td>0.72</td>
<td>0.71-0.74</td>
</tr>
<tr>
<td>Cotinine ≥3ng/ml</td>
<td>0.28</td>
<td>0.26-0.29</td>
</tr>
<tr>
<td><strong>Body mass index</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 30mg/M²</td>
<td>0.74</td>
<td>0.72-0.75</td>
</tr>
<tr>
<td>30mg/M² or more</td>
<td>0.26</td>
<td>0.25-0.28</td>
</tr>
<tr>
<td><strong>Comorbid conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0.85</td>
<td>0.84-0.86</td>
</tr>
<tr>
<td>Present</td>
<td>0.15</td>
<td>0.14-0.15</td>
</tr>
</tbody>
</table>
3.1.1 Weighted cannabis distribution

As represented in Figure 3, the pooled samples (2005-2012) show that 23.5%, 15.7%, 19.6%, and 16% of women within the age groups of 18-29, 30-39, 40-49, and 50-69, have reported regular use of cannabis (at least once a month), respectively. While 38%, 30%, 31%, and 30% of men within age groups of 18-29, 30-39, 40-49, and 50-69 have reported regular use of cannabis, respectively.

![Cannabis use distribution by age and gender](image)

Figure. 3: Weighted distribution of cannabis use (unweighted N= 20,150): NHANES 2005-2012

3.1.2 Cannabis parameters-depression association

3.1.2.1 Regular cannabis use

The main effects model has yielded the following significant variables (p<0.05): cannabis regular use, gender, cotinine level, education level, obesity, and comorbidity associated with depression. Also, after adjusting for comorbid conditions, age was no
longer significantly associated with depression. This can be explained by the increased prevalence and severity of comorbid conditions with aging. Spearman's correlation coefficient was estimated to assess the relationship between age and comorbidity and a moderate positive correlation was found (Spearman's rho = 0.4) which was statistically significant $p = 0.0001$. We generated logistic models incorporating self-reported smoking status (data not shown) that resulted in odds ratios similar to that measured by cotinine serum level.

Addition of interaction terms to the main effects model revealed significant interactions of gender with “regular cannabis use” $P=0.002$ and “body mass index” $P=0.008$. Therefore, two logistic regression models were created for men and women to estimate specific odds ratios based on gender. Tables 5 & 6 show the odds ratios for females and males, respectively
Table 5: Logistic regression model showing the association of depression and cannabis use, among females (NHANES 2005-2012; n= 10,293)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Adjusted odds ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabis use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular cannabis use</td>
<td>1.79</td>
<td>1.36 - 2.34</td>
<td>0.001</td>
</tr>
<tr>
<td>No use or non-regular use</td>
<td>1 (Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-39 years</td>
<td>1.22</td>
<td>0.86-1.75</td>
<td>0.2</td>
</tr>
<tr>
<td>40-49 years</td>
<td>1.28</td>
<td>0.90-1.8</td>
<td>0.1</td>
</tr>
<tr>
<td>50-69 years</td>
<td>1.20</td>
<td>0.86-1.6</td>
<td>0.2</td>
</tr>
<tr>
<td>18-29 years</td>
<td>1 (Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school graduate</td>
<td>0.62</td>
<td>0.45-0.84</td>
<td>0.003</td>
</tr>
<tr>
<td>Some college</td>
<td>0.57</td>
<td>0.42-0.77</td>
<td>0.001</td>
</tr>
<tr>
<td>College graduate or more</td>
<td>0.31</td>
<td>0.18-0.50</td>
<td>0.001</td>
</tr>
<tr>
<td>Less than high school</td>
<td>1 (Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cotinine level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 3 ng/ml</td>
<td>2.2</td>
<td>1.74 - 2.85</td>
<td>0.001</td>
</tr>
<tr>
<td>&lt; 3 ng/ml</td>
<td>1 (Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 30 kg/m²</td>
<td>1.82</td>
<td>1.39 - 2.39</td>
<td>0.001</td>
</tr>
<tr>
<td>&lt; 30 kg/m²</td>
<td>1 (Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbid conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Having comorbidity</td>
<td>1.74</td>
<td>1.40 - 2.15</td>
<td>0.001</td>
</tr>
<tr>
<td>No comorbidity</td>
<td>1 (Ref)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 6: Logistic regression model showing the association of depression and cannabis use, among males (NHANES 2005-2012; n=9,857)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Adjusted odds ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cannabis use</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular cannabis use</td>
<td>1.05</td>
<td>0.80 - 1.36</td>
<td>0.7</td>
</tr>
<tr>
<td>No use or non-regular use</td>
<td>1 (Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-39 years</td>
<td>1.20</td>
<td>0.8-1.58</td>
<td>0.5</td>
</tr>
<tr>
<td>40-49 years</td>
<td>1.07</td>
<td>0.674-1.71</td>
<td>0.7</td>
</tr>
<tr>
<td>50-69 years</td>
<td>1.32</td>
<td>0.89-1.94</td>
<td>0.1</td>
</tr>
<tr>
<td>18-29 years</td>
<td>1 (Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Education level</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school graduate</td>
<td>0.73</td>
<td>0.51 - 1.05</td>
<td>0.08</td>
</tr>
<tr>
<td>Some college</td>
<td>0.67</td>
<td>0.47 - 0.95</td>
<td>0.02</td>
</tr>
<tr>
<td>College graduate or more</td>
<td>0.26</td>
<td>0.15 - 0.45</td>
<td>0.001</td>
</tr>
<tr>
<td>Less than high school</td>
<td>0.73</td>
<td>0.51 - 1.05</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Cotinine level</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 3 ng ml</td>
<td>1.88</td>
<td>1.34 - 2.62</td>
<td>0.001</td>
</tr>
<tr>
<td>&lt; 3 ng/ml</td>
<td>1 (Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Body mass index</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 30 kg/m2</td>
<td>0.95</td>
<td>0.68 - 1.33</td>
<td>0.7</td>
</tr>
<tr>
<td>&lt; 30 kg/m2</td>
<td>1 (Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Comorbid conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Having comorbidity</td>
<td>2.17</td>
<td>1.48 - 3.18</td>
<td>0.001</td>
</tr>
<tr>
<td>No comorbidity</td>
<td>1 (Ref)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3.1.2.2 Cannabis use impact among users

Frequency of monthly cannabis use

The logistic model with frequency of cannabis use, as the main exposure variable, showed that the odds of having PHQ9 ≥ 10 is 1.22 (p=0.1, 95% CI=0.95-1.54) among those, who smoked cannabis ≥ 8 times a month, compared to those who used cannabis < 8 times a month of both genders (no significant interaction was found). This odds ratio was adjusted for gender, education level, and serum cotinine level, body mass index, and comorbid conditions. However, this odds ratio was not statistically significant (p= 0.1).

Cannabis daily dose

The number of joints smoked per day was assessed only in 2009-2010 and 2011-2012 cycles. The unweighted sample of those who smoked one joint, two joints, three to five joints and 6 or more joints was 742, 537, 420, and 113 respectively for a total of 1812.

The odds of having PHQ9 ≥ 10 among those who smoked six or more joints/day is 2.21 versus those smoked one joint/day, adjusting for gender, education level, cotinine level, body mass index, and comorbid conditions (p=0.03, 95 Cl=1.07-4.2). The odds ratios of having PHQ9 ≥ 10 among those who smoked two to five joints/day, compared to one joint a day, was 1.23 (p=0.2, 95 CI=0.86-1.75). There was no significant interaction between cannabis dose and gender.

The models with “cannabis use dose” and “regular cannabis use” yielded similar odds ratios and significance levels for gender, education level, cotinine level, body mass
index, and comorbid conditions as in the previous model, showing the association between regular cannabis use and depression.

3.1.2.3 Quitting cannabis use

Among people who ever tried to quit cannabis use, those who quit using cannabis for $\geq$ one month showed less odds of depression, compared to those who quit for $< 1$ month. The effect of quitting was stronger in females than males. Among females, the odds of depression decreased significantly ($p=0.009$, 95 CI=0.27 - 0.82) by 54% among those who quit using cannabis $\geq$ month, adjusting for education level, cotinine level, body mass index, and comorbid conditions, compared to those who quit for $< 1$ month. Among males, the odds of having PHQ9 $\geq$ 10 decreased only by 32% ($p=0.2$, 95 CI=0.31 - 1.07) among those who quit cannabis use $\geq$ one month, adjusting for education level, cotinine level, body mass index, and comorbid conditions, compared to those who quit for $< 1$ month.

3.2 Antidepressant medications

Table 7 and figure 4 show the weighted frequency of administration of antidepressant medications drawn from NHANES 2005-2012 cycles. Figure 5 compares the weighted percentage of PHQ9 $\geq$ 10 to the weighted percentage of antidepressant medication intake.
Table 7: Weighted distribution (percentage) of antidepressant use (NHANES 2005-2012; unweighted n=20150).

<table>
<thead>
<tr>
<th>Age</th>
<th>Regular cannabis users</th>
<th>Non users or non-regular cannabis users</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>Proportion 95% CI</td>
</tr>
<tr>
<td>Females</td>
<td>1.6</td>
<td>0.08 – 2.4</td>
</tr>
<tr>
<td>Males</td>
<td>0.07</td>
<td>0.01-1.3</td>
</tr>
</tbody>
</table>

NB: cannabis missing observation were imputed using MICE
Figure 4: Weighted distribution of antidepressant use (NHANES 2005-2012; unweighted n=20150)

NB: Data on age and medication were complete (were not imputed)
Logistic regression showed no significant association between cannabis use and intake of antidepressant medications. The odds of regular cannabis use was 0.81 among women receiving antidepressant medications, compared to those who did not receive the medications (95% CI=0.21-3.1, p=0.50). The odds of regular cannabis use was 1.87 among men receiving antidepressant medications compared to those who did not receive antidepressant medications (95% CI=0.44-7.9, p=0.50).

Logistic regression also revealed no significant association between quitting cannabis use and antidepressant intake. The odds of quitting cannabis for one month or more increased by 80% among individuals receiving antidepressant medications (p=0.2).
3.3 Temporal trend of regular cannabis use, depression, and cotinine level across NHANES cycles (2005-2012)

Tables 8 & 9 and figure 6 show the weighted prevalence of depression, regular cannabis use, and cigarette smoking status (measured by serum cotinine level) in both genders. The prevalence of depression and tobacco smoking peaked, in both genders, in the 2007-2008 cycle. On the other hand, regular cannabis use showed the lowest prevalence, in both genders, in the 2007-2008 cycle.

Table 8: Weighted prevalence of regular cannabis use, PHQ9 ≥ 10, and cotinine serum level ≥ 3 ng/ml among females (NHANES 2005-2012)

<table>
<thead>
<tr>
<th>NHANES cycle</th>
<th>PHQ9≥ 10</th>
<th>Regular cannabis</th>
<th>Cotinine ≥ 3ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005-2006</td>
<td>6.7%</td>
<td>17%</td>
<td>20%</td>
</tr>
<tr>
<td>2007-2008</td>
<td>10.1%</td>
<td>15.5%</td>
<td>29.6%</td>
</tr>
<tr>
<td>2009-2010</td>
<td>9.7%</td>
<td>19.9%</td>
<td>19%</td>
</tr>
<tr>
<td>2011-2012</td>
<td>9.4%</td>
<td>20.7%</td>
<td>17.3%</td>
</tr>
</tbody>
</table>
Table 9 Weighted prevalence of regular cannabis use, PHQ9 ≥ 10, and cotinine serum level ≥ 3 ng/ml among males (NHANES 2005-2012).

<table>
<thead>
<tr>
<th>NHANES cycle</th>
<th>PHQ9 ≥ 10</th>
<th>Regular cannabis</th>
<th>Cotinine ≥ 3ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005-2006</td>
<td>5.1%</td>
<td>24.2%</td>
<td>29.5%</td>
</tr>
<tr>
<td>2007-2008</td>
<td>7.1%</td>
<td>22.3%</td>
<td>29.6%</td>
</tr>
<tr>
<td>2009-2010</td>
<td>7.0%</td>
<td>27.1%</td>
<td>26.3%</td>
</tr>
<tr>
<td>2011-2012</td>
<td>6.8%</td>
<td>27.5%</td>
<td>25.6%</td>
</tr>
</tbody>
</table>
Figure 6: Weighted prevalence of regular cannabis use, PHQ9 ≥ 10, and cotinine serum level ≥ 3 ng/ml (unweighted n=20,150): NHANES 2005-2012

NB: The pooled frequency of cannabis use for 2005-2008 differed significantly from the pooled frequency for 2009-2012 (p=0.035).
3.4 Cannabis use association with cardiovascular diseases

Direct acyclic graph (DAG) (Figure 7) shows the association between cannabis and cardiovascular diseases.

![DAG diagram showing the association between cannabis and cardiovascular diseases](image)

**Figure 7: Cannabis and cardiovascular diseases association**
As shown in table 10, the odds of cardiovascular disease among regular cannabis users was 1.07 (95% CI=0.82-1.40), compared to non-users, controlling for age, gender, race, education level, cotinine level, body mass index, and diabetes mellitus. This odds ratio was not statistically significant.
Table 10: Logistic regression model showing the association of cannabis with cardiovascular diseases (NHANES 2005-2012; n=20,150)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabis use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular cannabis use</td>
<td>1.07</td>
<td>0.82 - 1.40</td>
<td>0.6</td>
</tr>
<tr>
<td>No use or non-regular use</td>
<td>1 (Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.47</td>
<td>1.30 - 1.70</td>
<td>0.001</td>
</tr>
<tr>
<td>Female</td>
<td>1 (Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-39 years</td>
<td>1.9</td>
<td>1.19 - 3.1</td>
<td>0.009</td>
</tr>
<tr>
<td>40-49 years</td>
<td>5.4</td>
<td>3.5 - 8.1</td>
<td>0.001</td>
</tr>
<tr>
<td>50-69 years</td>
<td>13.4</td>
<td>8.9 - 20.2</td>
<td>0.001</td>
</tr>
<tr>
<td>18-29 years</td>
<td>1 (Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanics</td>
<td>0.62</td>
<td>0.51 - 0.771</td>
<td>0.001</td>
</tr>
<tr>
<td>Whites</td>
<td>0.84</td>
<td>0.71-0.98</td>
<td>0.03</td>
</tr>
<tr>
<td>Others</td>
<td>0.96</td>
<td>0.71 -1.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Blacks</td>
<td>1 (Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school graduate</td>
<td>0.68</td>
<td>0.54- 0.86</td>
<td>0.002</td>
</tr>
<tr>
<td>Some college</td>
<td>0.65</td>
<td>0.51- 0.82</td>
<td>0.001</td>
</tr>
<tr>
<td>College graduate or more</td>
<td>0.49</td>
<td>0.36-0.67</td>
<td>0.001</td>
</tr>
<tr>
<td>Less than high school</td>
<td>1 (Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHQ9≥10</td>
<td>2.2</td>
<td>1.8-2.7</td>
<td>0.001</td>
</tr>
<tr>
<td>PHQ9&lt;10</td>
<td>1 (Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cotinine level in women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 3 ng/ml</td>
<td>2.1</td>
<td>1.54-2.87</td>
<td>0.001</td>
</tr>
<tr>
<td>&lt; 3 ng/ml</td>
<td>1 (Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cotinine level in men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 3 ng/ml</td>
<td>1.14</td>
<td>0.86-1.49</td>
<td>0.3</td>
</tr>
<tr>
<td>&lt; 3 ng/ml</td>
<td>1 (Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 30 kg/m²</td>
<td>1.67</td>
<td>1.43-1.95</td>
<td>0.001</td>
</tr>
<tr>
<td>&lt; 30 kg/m²</td>
<td>1 (Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (DM)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Having DM</td>
<td>3.05</td>
<td>2.49 - 3.74</td>
<td>0.001</td>
</tr>
<tr>
<td>No DM</td>
<td>1 (Ref)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Chapter 4: Discussion

4.1 Cannabis use and depressive symptoms

In this study we sought to explore the association between cannabis and depressive symptoms \((\text{PHQ9} \geq 10)\) controlling for different confounding factors. Our results indicate significant gender differences in the association between depressive symptoms and cannabis regular use. While women reported lower rates of cannabis use than men, women who used cannabis regularly had higher odds of depressive symptoms compared to women who did not use cannabis, adjusting for socio-demographic and clinical variables. This effect was not present among men.

Pharmacokinetics and pharmacodynamics depend on the metabolic rate, body size, fat and water body contents, and sex hormones (Carroll, et al. 2004). Gender differences in pharmacokinetics might be attributed to the effects of sex hormones. Data from clinical and preclinical studies of substance use disorders have suggested that females are more vulnerable than men to the deleterious effects of different drugs (Winsauer, et al. 2011; Zhang, et al. 2008). Animal research has shown that there are sex differences in the functioning of the endocannabinoid system, where THC and other cannabinoids exert their actions (Wakley, et al. 2014).

A study was conducted to determine whether or not gonadal hormones could modulate THC dependence in adult rats. This study has found that testosterone and estradiol produce opposite effects on THC-induced behavior among male and female rats.
Estradiol and progesterone in females have shown greater tolerance to THC-induced locomotor suppression, increased withdrawal-induced chewing, and progesterone increased withdrawal-induced sniffing. On the other hand, Testosterone in males has shown to decrease withdrawal-induced licking (Marusich, et al. 2015). Another study has compared measures of cognitive performance between groups of adult intact or ovariectomized female rats that had received THC. The intact group of female rats has shown a lower response rate on measures of learning and performance as compared to ovariectomized group (Winsauer, et al. 2011).

Clinical studies have suggested that teenage girls who use marijuana may have a higher risk of brain structural abnormalities as a result of regular marijuana exposure than teenage boys. In their study, Medina and Collogues recruited 16-18-year old regular cannabis users (n=16) and controls (n=16) and performed a high-resolution anatomical magnetic resonance brain imaging for all participants. They have found that, after controlling for lifetime alcohol use, gender, and intracranial volume, regular cannabis users did not differ from controls in prefrontal cortex (PFC) volume. However, group-by-gender interaction was observed; female regular cannabis users demonstrated larger PFC volumes compared to female controls. The study has concluded that, given the relationship between larger PFC total volumes and poorer executive functioning among cannabis users, female cannabis users may be at a higher risk for neurocognitive consequences (Medina, et al. 2009). These observations came in accordance with our observation that shows gender differences in the association between depressive symptoms and cannabis regular use. Similar observations were shown by McQueeny et
al. when they have used a high-resolution magnetic resonance imaging system to scan the brains of 16-19-year old group of 35 marijuana users and 47 controls. They have found that female marijuana users had a larger right amygdala (the integrative center for emotions, emotional behavior, and motivation) volume than female controls. However, male users had similar volumes as male controls. It is of note that internalizing behavior problems (i.e., anxiety, depressive, withdrawal symptoms) have been associated with a larger right amygdala, compared to controls (McQueeny, et al. 2011).

Our study has found that, among cannabis users, heavy use of cannabis (6+ joints per day) was significantly associated with increased odds of depressive symptoms, compared to light use (1 joint per day) in both genders. In accordance with our finding, several studies have shown a positive association between cannabis use and depression. For instance, animal and human research have suggested that the prefrontal cortex may be particularly vulnerable to the effect of heavy marijuana use, which explains the increased risk of depression and cognitive deficit (Lemos, et al. 2010; Shollenbarger, et al. 2015). Rasic et al. have conducted a longitudinal study to look at whether or not there is a dose response association between cannabis use and depression, and they have found a positive correlation between cannabis dose and risk of depression (Rasic, et al. 2013). A significant dose-response relationship was reported when lightest and heaviest marijuana user groups were tested for neurocognitive performance. Within the same line, heavy marijuana use was associated with a lower performance on tests of memory, executive functioning, and manual skills. Several studies showed that heavy marijuana users perform less effectively than the light users they when tested for verbal learning.
memory, and reaction time (Bolla, et al. 2002; Pope and Yurgelun-Todd 1996; Solowij, et al. 2002). As the cognitive and motor functions are largely controlled by the hippocampus, prefrontal cortex, and cerebellum regions of the brain, it is important to note that Tetrahydrocannabinol has been shown to cause deleterious effects on these important brain structures (Herkenham, et al. 1990).

For the first time, our study suggested that quitting cannabis for more than a month tends to improve the depressive symptoms, particularly among women. Several studies have shown the same observation when they tested the effect of quitting cannabis on other mental illness. For instance, a longitudinal study has investigated the effect of quitting cannabis on bipolar disorder and found that bipolar patients, who stopped using cannabis during mixed episode (manic mixed with major depressive episode) have presented similar clinical and functional outcomes to never users. The continued use was associated with higher risk of recurrence and poorer functioning (Zorrilla, et al. 2015). Bonnet and colleagues have investigated the impact of inpatient detoxification treatment on psychiatric symptoms of chronic cannabis addict patients. In their prospective study, they have found that inpatient cannabis detoxification treatment significantly improved psychiatric symptoms (Bonnet, et al. 2015). On the contrary, one study has found that very heavy use of marijuana is associated with persistent decrements in neurocognitive performance even after 4 weeks of abstinence (Bolla, et al. 2002). It is important to note that the study participants were followed up only for 28 days so, it is unclear if these decrements will resolve with continued abstinence. Tobacco cessation has been shown to improve depressive symptoms of smokers. In their meta-analysis, Taylor
et al, have found that smoking cessation is associated with reduced depression, anxiety, and stress and improved positive mood and quality of life compared with continuing to smoke (Taylor, et al. 2014). Although tobacco smoking and marijuana have different mood of actions, they both have shown to be associated with depressive symptoms.

4.2 Antidepressant medications

While we found a significant association between cannabis use and depressive symptoms, when depression was used as an outcome variable, such an association was not found when we used the antidepressants as dependent variable. This finding can be explained by the fact that people who seek medical care, due to depressive symptoms, are less likely to self-medicate by using cannabis. Also, antidepressant medication may have eliminated the depressive symptoms which motivated individuals to quit smoking.

Thirdly, due to a potential pharmacological interaction between tricyclic antidepressants (TCAs) and cannabis, there is a possibility that using cannabis with TCAs may lead to unpleasant effects such as tachycardia, hypertension, and confusion. Having such complications might motivated individuals to stop smoking cannabis (Kizer 1980).

There is a plausible interaction between cannabis and other categories of antidepressants as specific serotonin reuptake inhibitor, serotonin-norepinephrine reuptake, and monoamine oxidase inhibitors. This interaction might happen probably because of the dopaminergic effect of cannabis, leading to unpleasant side effects such as tachycardia and elevated blood pressure. However, there is no published research that looked at pharmacological interaction.
Our findings suggest that a high proportion of those who experience depressive symptoms tend not to seek help. In accordance with our finding, a previous study has found that only 33.6% of respondents, meeting 12-months major depression criteria, used antidepressant medications and only 44.3% used psychotherapy (Gonzalez, et al. 2010). This study has utilized the National Institute of Mental Health's Collaborative Psychiatric Epidemiology Surveys (CPES) data to look at the gap between mental illness and treatment. In this survey, depression was assessed using Quick Inventory of Depressive Symptomatology Self-Report (Rush, et al. 2003). Another systematic review has found that only 18 to 34% of young people with high levels of depression or anxiety symptoms seek professional help (Gulliver, et al. 2010). Several studies have attempted to explain why patients with depressive symptoms tend not to seek medical help. The stigma of mental illness has often been considered a potential cause for reluctance in seeking help (Schomerus and Angermeyer 2008). Lack of confidentiality and trust with respect to the potential source of help have been reported as major barrier (Rickwood, et al. 2007). Within the same line, a study has shown that general practitioners are not considered as an appropriate source of help for mental disease (Kelly, et al. 2007). Furthermore, studies have shown that lack of accessibility of mental health professionals, particularly in rural communities, is a barrier for patients to seek help (Fox, et al. 2001). Difficulty of identifying the symptoms of mental illness has also been reported as a barrier to mental health help seeking (Gulliver, et al. 2010).
4.3 Temporal trends in prevalence of cannabis use and depression from 2005 through 2012

Our finding showed that in 2007-2008 (during the economic recession) was accompanied by a significant increase in depressive symptoms prevalence in the US population. We have also found that tobacco smoking has increased to its peak in 2007-2008 NHANES cycle then dropped steadily in the following cycles.

Our observation of increased depressive symptoms in 2008 was also observed by Mehta et al. in their analysis of National Health and Nutrition Examination Survey data (Mehta, et al. 2015).

In the same line with our finding, a previous study has demonstrated that the sales records of tobacco companies showed an increase during the economic crises in 2008. The study has also reported that smokers not only continued to smoke but also actually increased their tobacco intake (He and Yano 2009). Bosetti et al. have utilized data from the repeated Behavioral Risk Factor Surveillance System (BRFSS) that surveyed the pre-crisis (2005–2007) and post-crisis (2009–2010) periods to determine the effects of the 2007-2008 economic crisis on smoking prevalence in the USA. The study have found that the economic crisis accounted for 1.5% increase in cigarette smoking, particularly among unemployed individuals (Gallus, et al. 2015). This increased rate of smoking cigarettes was probably to cope with job loss and unemployment-induced stress. As job loss and unemployment can induce significant stress, the observation that the increase of cigarettes use further supports the strong correlation between tobacco smoking and depressive symptoms.
While tobacco consumption increased to its peak in 2008, cannabis use dropped to its lowest level. One study has measured the illicit drug consumption in the general population by repeatedly analyzing samples from a raw wastewater of two cities in Northern Italy, Milan and Como, from 2005 to 2009. This study has found that THC concentration wastewater dropped in 2008, compared to 2005 then rose significantly from March to September 2009 and reached to the levels previously seen in 2005 (Zuccato, et al. 2011). This finding is probably explained by the consumers’ financial difficulties caused by the economic crisis.

4.4 Cannabis use and cardiovascular diseases

Our analysis does not show a significant association between cannabis use and cardiovascular events. There aren’t definitive, rigorous studies that investigated this association. Nonetheless, previous studies have raised the issue of the possible implication of cannabis in cardiovascular outcome. Mac et al have shown that oral treatment with a low dose of THC inhibits atherosclerosis progression in a mouse model. They have proposed that THC or cannabinoids may be valuable targets for treating atherosclerosis through the activation of the CB2 receptor (Steffens, et al. 2005). Muller and colleagues interviewed 3882 patients with acute myocardial infarction within an average of 4 days after infarction onset. Only 0.09% reported smoking marijuana within the prior 24 hour. Another 0.02% reported marijuana use within 1 hour prior to myocardial infarction symptoms. The study has concluded that cannabis might be a rare trigger for myocardial infarction (Mittleman, et al. 2001). On the contrary, a French study has identified all spontaneous reports of cardiovascular
complications related to cannabis use collected by the French Addictovigilance Network. They have found that 1.8% of all cannabis-related reports (35/1979) were cardiovascular complications, with patients being mostly men (85.7%) and of an average age of 34.3 years. All of those complications were of acute nature such as acute coronary syndromes, peripheral arterial complications as thromboangiitis obliterans, and cerebral complications. In 0.4%, the event led to patient death. The study has mentioned that cardiovascular complication might be underestimated due to underreporting of cannabis use (Jouanjus, et al. 2014).
Chapter 5: Conclusion

Regular cannabis use (at least once per month) among women was associated with depressive symptoms. Furthermore, heavy cannabis use (six joints per day) was associated with depressive symptoms among both men and women. Depressive symptoms tend to improve in both men and women following quitting cannabis for more than one month; however this improvement was more prominent among women. Our study is cross sectional in nature, therefore, we could not establish temporality and future research, of longitudinal nature, is required.

We have found a significant association between cannabis use and depressive symptoms when depression was used as an outcome variable. Such an association was not found when we used the antidepressants as dependent variable. As depression may occur first and lead to cannabis use, proper screening and treatment with antidepressant medications will help to reduce or control the escalating cannabis use problem.

Our findings have found that a high proportion of people with depression are not receiving treatment. This problem has to be addressed through correcting barriers and obstacles of seeking treatment among people with depressive symptoms.

Depressive symptoms have increased significantly in 2007-2008 NHANES cycle compared to 2005-2006 NHANES cycle, then dropped slightly in the following cycles (2009-2012). Interestingly, cannabis use pattern has shown inverse correlation with depressive symptoms pattern as it dropped in 2007-2008 cycle compared to 2005-2006
cycle, then rose again in the following cycles. Decriminalization of marijuana in some states may have contributed to this rise following the financial crises in 2008. On the other hand, tobacco smoking use, measured by serum cotinine, has shown the same pattern of increase similar to that shown with depressive symptoms. The economic crisis in 2008 might be linked to these findings as individuals tried to ease their stress symptoms through cigarette smoking, which is much cheaper than cannabis.

The steady increase in cannabis use after 2008 is alarming and requires careful attention and perhaps more restricted policy measures and public health effort to solve the problem of illicit cannabis use or at least to stop the progression of such a socio-economic health problem.

We have not found an association between cannabis use and cardiovascular events even among heavy users; however, this observation warrants further investigations.

Public Policy should encourage routine screening of depression, like screenings for other diseases, in the primary care clinics. The escalating cannabis use has to be addressed by developing programs helping people to quit using cannabis, particularly among women.
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